



# Thyroid Eye Disease

Where Are We Now and  
Where Are We Going?

# Thyroid Eye Disease

## Where Are We Now and Where Are We Going?

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This initiative was sponsored by Amgen. The roundtable meeting featuring eight expert faculty was planned and hosted by Amgen in collaboration with the meeting co-chairs, Dr Mario Salvi and Mr Jimmy Uddin. This paper, titled *'Thyroid Eye Disease: Where Are We Now and Where Are We Going?'*, was developed in partnership with Medscape Medical Affairs and is based on the roundtable discussions.

# Context

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A virtual roundtable meeting conducted at the beginning of December 2024 convened a multidisciplinary faculty of endocrinologists and ophthalmologists with recognized expertise in the treatment of thyroid eye disease (TED).

The patient perspective was represented by the president of the Italian Association of Basedow and Thyroid Patients (AIBAT), herself a person living with TED.

These experts were asked to reflect on the multidimensional burden of TED, its pathophysiology and treatment (outside the US), and how best to raise awareness and improve the diagnosis and management of this under-served disease among their peers.

**This paper captures these expert insights to create an urgent call to action: to improve healthcare practitioner knowledge regarding TED to hasten the appropriate referral and specialist treatment of this potentially devastating disease.**

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# Executive Summary

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TED is an autoimmune condition that affects approximately 1 in 1,000 people in Europe and occurs more frequently in women than in men. It develops in approximately 40% of patients with Graves' disease. One of the main mechanisms contributing to the development of TED may be the activation of the insulin-like growth factor-1 receptor (IGF-1R) pathway. IGF-1R is overexpressed on orbital fibroblasts, where its activation is thought to result in inflammation, tissue expansion, and swelling and remodeling of the muscle and fat behind the eye / in the orbit. The resultant manifestations of TED can vary widely, with the most common symptoms being upper eyelid retraction, proptosis (eye bulging), and diplopia (double vision). In severe cases, TED can progress to dysthyroid optic neuropathy, a serious complication that may threaten vision. Diplopia and orbital pain affect day-to-day functioning, while proptosis can have a substantial cosmetic impact, leading to social isolation and loss of self-confidence. Despite the substantial psychosocial burden of TED, there are limited data on its related indirect (and direct) costs, although significant associations have been reported between work disability and diplopia, optic neuropathy, and proptosis.

Management and treatment of TED should be tailored to the patient's symptoms, clinical signs and disease phenotype, with a focus on normalizing thyroid dysfunction, reducing inflammation, improving diplopia and proptosis (if present), and optimizing quality of life (QOL), preferably within a multidisciplinary setting and early in the disease course. Patients with TED should have their medical and surgical options explained to them, including potential outcomes and how long treatment may last – this will improve adherence and patient engagement. TED is often under-recognized among general physicians, as well as among endocrinologists and ophthalmologists without specialized expertise in TED; this may lead to delays in diagnosis and suboptimal management. Expanded awareness of TED will increase its early identification, rapid referral, and appropriate targeted treatment.

Treatment for TED is currently not optimal as it relies on non-specific medications that address only some of its symptoms and signs. Recent years have seen significant steps forward in our understanding of

TED pathophysiology, permitting development of targeted therapies and raising hope for improved outcomes. Patients with TED should be offered the opportunity to participate in clinical trials and be given practical information about where and how to enroll.

# What is TED and What is its Relationship to Graves' Disease?



## MR JIMMY UDDIN:

TED is heterogeneous with different phenotypes reflecting the variable underlying pathophysiology of the disease.

Graves' disease — a chronic, thyroid-specific autoimmune disease — is the most common cause of hyperthyroidism and results from thyroid stimulating hormone receptor antibodies (TSHR Ab or TRAb) targeting the thyroid gland and inducing excessive thyroid hormone secretion.<sup>1</sup> TED primarily targets the orbital tissue behind the eye and is the most frequent extrathyroidal manifestation of Graves' disease, developing in approximately 40% of patients,<sup>2</sup> although approximately 10% of patients with TED have hypothyroidism (e.g., Hashimoto's thyroiditis) or are euthyroid.<sup>3</sup> In general, TED presents at the same time as Graves' disease but can also precede its diagnosis or develop later in its disease course.<sup>4</sup> The first step in treating Graves' disease and TED is shared, namely normalizing thyroid function with anti-thyroid drugs;<sup>5,6</sup> however, TED and Graves' disease are distinct conditions and require separate treatment.<sup>4</sup>

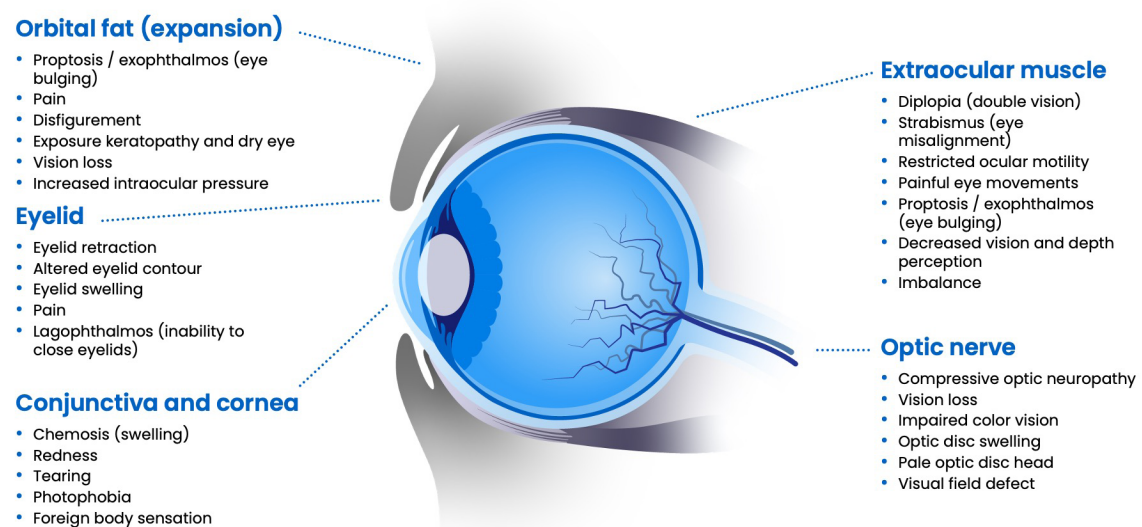
The pathophysiological relationship between Graves' disease and TED has not been fully characterized, although it is thought that binding of TRAb to TSHR expressed in orbital tissues may trigger adipogenesis in TED.<sup>4,7</sup> IGF-1R is a receptor tyrosine kinase that has a critical role in cell growth and differentiation.<sup>8</sup> IGF-1R is overexpressed on key effector cells in TED, including orbital fibroblasts, the stimulation of which results in inflammation, tissue expansion, and swelling and remodeling of the muscle and fat behind the eye.<sup>4,7,9</sup> In individuals with TED, stimulatory IGF-1R autoantibodies activate IGF-1R, which also participates in receptor-receptor crosstalk with TSHR in orbital tissues.<sup>10-12</sup>

The occurrence of TED in patients who are euthyroid appears contradictory; however, this finding may be related to timing, follow-up, and assay limitations. Clinical experience indicates that patients with classical TED and apparently normal thyroid function may

develop thyroid autoantibodies months or even years later, indicating subclinical autoimmune activity. Additionally, low antibody assay sensitivity may fail to detect low-level immune involvement leading to an underestimation of thyroid autoimmunity in these patients.

TED affects approximately 1 in 1,000 people in Europe and occurs more frequently in women than in men;<sup>13</sup> smoking is the main risk factor.<sup>5</sup> Suspicion of TED is raised based on clinical signs and symptoms, the most common being upper eyelid retraction (~90% of patients),<sup>3</sup> eye bulging / protrusion (proptosis, in ~60% of patients),<sup>3</sup> and double vision (diplopia, in ~50% of patients).<sup>14</sup> Between 30 and 60% of patients with TED report pain and discomfort.<sup>3,14</sup> Other signs include tearing, restricted eye motility, eye misalignment (strabismus) and vision loss resulting from orbital fat expansion or compression of the optic nerve<sup>15,16</sup> (Figure 1).

**Figure 1. Clinical signs and symptoms of TED<sup>15,16</sup>**



TED commonly presents bilaterally. However, about 15% of patients with TED have a purely unilateral presentation, which progresses to the contralateral eye over time in approximately 15% of these individuals.<sup>17</sup> The clinical activity score (CAS) can be used to assess disease activity and severity based on symptoms and signs indicative of inflammation, with a score of  $\geq 3$  at presentation suggesting active TED.<sup>5</sup>

Certain biochemical changes are indicative of TED caused by hyperthyroidism, including suppressed TSH, elevated TRAb, and increased free T3 or T4 (triiodothyronine and thyroxine) levels.<sup>18</sup> Patients with a more severe TED disease course are more likely to have higher

circulating TRAb titers, particularly when based on stimulatory TRAb measurements at first presentation.<sup>19-21</sup> However, this relationship depends on the specific antibodies being measured; for example, measuring binding TRAb titers only without distinguishing between stimulatory, blocking, or neutral TRAbs may be misleading in terms of likely disease progression.<sup>22</sup>

Magnetic resonance imaging and computed tomography are important diagnostic tools for the identification of the classical features of TED, such as extraocular muscle enlargement and orbital fat expansion.<sup>5</sup> Imaging is key when investigating unilateral eye manifestations, which occur more often in patients with TED who are euthyroid or hypothyroid<sup>23</sup> and may be indicative of orbital issues other than TED (sarcoidosis or orbital lymphoma, for example).<sup>24</sup> It is important to note that TED is heterogeneous in its pathophysiology, manifestations, disease course, and therapeutic response<sup>25</sup> and that some patients may have severe disease with little proptosis and vice versa. Furthermore, clinical signs differ in patients with classical TED compared with patients who have TED but are euthyroid or hypothyroid.<sup>23</sup> In general, however, clinical assessment of a patient provides the strongest diagnostic evidence for TED and should receive greater weighting than the results of single blood tests or antibody assays.

# What is Known About the Psychosocial Impact of TED?

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## EMMA'S PATIENT EXPERT PERSPECTIVE:

Many patients become disabled by this terrible illness, some cannot work and are forced to retire prematurely. They have issues with other activities too, when they drive or when they are in front of a computer. Diplopia is a big problem, but the disease also causes tearing, redness, and retraction of the eyelids. Then TED transforms their faces – it's traumatic and changes their relationships and connections; they become ashamed to meet and talk to other people. From the onset of TED, I received specialist treatment, but I still didn't have the courage to look in the mirror because my face had been utterly altered and I didn't recognize myself.

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## DR JULIETTE ABEILLON:

The functional and aesthetic impacts of TED both influence QOL – and this influence is not necessarily proportional to the severity of disease.

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The visual and physical limitations imposed by TED can impede patients' daily activities, QOL, and ability to work,<sup>26-28</sup> with diplopia and orbital pain having a particularly detrimental effect on functioning, mobility, reading (including of a smartphone or laptop), and independence.<sup>27</sup> In individuals with multiple life-altering TED symptoms, some interventions must be prioritized before others and patients may be left waiting long periods for multiple sequential procedures. TED manifestations, particularly proptosis, can also have a substantial cosmetic impact, leading to social isolation and loss of self-confidence.<sup>26</sup> These functional and aesthetic changes can affect patients in a way that is disproportionate to the severity of disease.<sup>29</sup>

QOL and mental health is decreased in individuals with TED compared with the general population, patients with Graves' disease without TED, and patients with other chronic diseases, such as diabetes.<sup>26,27,30</sup> Overall, 40% and 24% of patients with TED experience anxiety and depression,

respectively,<sup>27</sup> and patients with TED are 2.7-times more likely to die by suicide compared with the general population.<sup>31</sup>

The above findings are borne out by a recent survey conducted by the French patient advocacy group, Vivre Sans Thyroïde (VST), the interim results of which were presented at the 2024 French Society of Endocrinologists (SFE) National Congress.<sup>32</sup> Interim feedback from 103 patients with TED regarding disease burden reported that 90% of patients had a loss of self-confidence, 70% experienced loss of autonomy, 60% felt socially isolated, and 60% experienced an impact on their emotional life. Furthermore, 11% reported that their relationship had broken down and that this was directly related to TED. More than 50% of patients felt sadness and anxiety; however, only 20% received psychological support.<sup>32</sup>



#### **PATIENT PERSPECTIVES OF VST SURVEY PARTICIPANTS:**

The most difficult thing is to accept that there will be no return to the situation as it was before the disease, not only in terms of the purely aesthetic aspect of the eyes (even with surgery), but also in all aspects of life (emotional, psychological, and physical). Psychological support is essential in this disease, and we don't say this enough. For my part, when I was diagnosed, I had no idea what it would entail and that my life would be irreparably affected.

It's very difficult to live with the constant discomfort and the physical change. I shut myself off a lot, I still work but I only see my loved ones and I don't go out anymore.

The psychological effects of TED can be overlooked by physicians who may focus instead on clinical measures. A disconnect between the treatment goals most important to patients and clinicians can result in non-adherence and loss to follow-up. Two reliable questionnaires can be used to measure QOL in patients with TED: the Thyroid Eye Disease Quality of Life scale (TED-QOL, comprising three questions each with a 10-point Likert scale;<sup>33</sup> Figure 2) and the Graves' Ophthalmopathy Quality of Life questionnaire (GO-QOL, comprising 16 questions, eight concerned with function and eight concerned with appearance, all measured using three-point Likert scales).<sup>34</sup> TED-QOL is the simpler tool and may be useful in everyday clinical situations. GO-QOL provides a more detailed analysis for use during research and has been validated across several cultures and languages.

Figure 2. TED-QOL questionnaire<sup>33</sup>

Please circle the number that best describes your position

1) How is your eye disease currently interfering with your **overall quality of life**?



2) How is your eye disease currently affecting your **ability to carry out daily activities**?



3) How is your eye disease currently affecting your **satisfaction with your appearance**?



#### EMMA'S PATIENT EXPERT PERSPECTIVE:

Patients experience great difficulty living with proptosis and diplopia, due to work issues and psychological problems. A striking example is that of a close colleague in the Italian Patient Association who developed severe proptosis and was left by her partner shortly before their wedding. She had serious problems with depression as a result. Among many testimonies, I particularly remember a letter from the husband of a TED patient based in the US. His wife previously had an open and communicative character, but she was affected by TED and treated with mixed results. These experiences changed her, and she was never the same afterwards, with moods alternating from recurring anxiety to pessimism.

# Can Treatment of TED Improve Patients' QOL?

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## DR JULIETTE ABEILLON:

Our current treatments are mostly judged by their effect on clinical activity, but QOL is majorly linked to sequelae. We need to be clear about what the goals of treatment are from the beginning and at every step to improve adherence to treatment and QOL.

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Data from randomized trials using the GO-QOL questionnaire have shown that three medications improve QOL in patients with TED, namely intravenous (IV) steroids, selenium, and teprotumumab (the latter is not approved by the EMA at the time of publication).<sup>35</sup> The impact of surgery on the QOL of patients with TED is complex. While surgery, particularly orbital decompression, improves psychosocial outcomes, drug treatment may have a similar impact and duration of effect on QOL.<sup>36</sup> Surgical procedures have associated risks and complications (e.g., periorbital ecchymosis and edema, hemorrhage, infection, and residual visual field defects)<sup>37</sup> as well as a psychological burden, and may not be accepted by all patients because of fear or cultural stigma. Survey data from the US reveal that patients with TED who undergo multiple procedures (such as orbital decompression, strabismus correction, and cosmetic procedures) have significantly lower GO-QOL scores than patients who have not received surgery.<sup>38</sup> These patients are obviously those with more severe TED, but there is a probable direct impact of multiple surgeries on QOL. Managing patient expectations around the outcomes and duration of such procedures (and TED treatment in general) may ameliorate the associated QOL burden. It should also be emphasized to patients that modern surgeries for TED have low complication rates.



## PROF. DIEGO STRIANESE:

Incidence of anxiety and disappointment is elevated in patients who have multiple surgeries – this may mean that sometimes surgeries are not exactly matching the expectations of the patient. It is important that patients understand that surgical therapy, particularly decompression, improves appearance in the majority of cases but a complete 'restitutio ad integrum' is rarely possible.

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Conversely, not all patients have a strong aversion to surgeries, indeed within the faculty's clinical experience, a significant group of patients with TED express gratitude for any improvement afforded by orbital decompression in terms of strabismus and eye pressure. Aesthetic rehabilitation surgery is also welcomed by some patients. Life is now lived increasingly online through the prism of social media, which has elevated the importance of appearance to many. Individuals may request procedures to correct what clinicians perceive to be symptoms of mild TED (minimal eyelid retraction, tearing) to allow them to look and function as they have previously. Whether these shifting expectations will impact future clinical trial design and endpoints remains to be seen.



#### **EMMA'S PATIENT EXPERT PERSPECTIVE:**

It is important to inform patients realistically about the treatment path they must take. Our patient association tries to do this, providing information and comparing itineraries and experiences. I underwent orbital decompression, a crucial moment in the resolution of TED (I had significant proptosis). Our association also illustrates the steps, risks, problems, and recovery times related to surgeries, although these procedures are not necessary for all patients with TED. In my case, the surgery was successful and my QOL has improved considerably.

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# What Are the Costs of TED in Terms of Lost Productivity?

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## PROF. DR KATHARINA PONTO:

There is a close relationship between work impairment and QOL as measured with the GO-QOL questionnaire. Low scores on the two subscales of the GO-QOL indicate patients who need psychological support and who experience work impairment.

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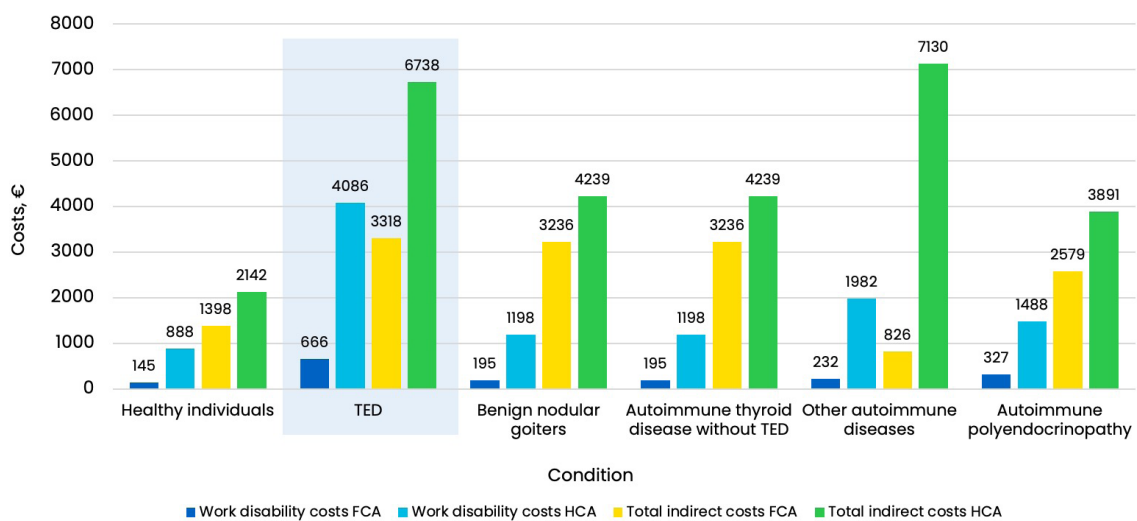
Far from being a predominantly cosmetic disease, the physical and psychological impacts of TED are substantial, with far-reaching consequences. Currently there are limited data on the indirect costs of TED, although these are likely to be considerable owing to patients' reduced work capacity as a result of their symptoms. In a prospective study of 310 consecutive patients with TED at a multidisciplinary center in Germany, 22% and 6% of employed patients (n=215) were temporarily or permanently work disabled and 2% had lost their jobs.<sup>28</sup> The whole-life burden of TED must also be considered; affected patients may not regain their original level of function, and ongoing morbidity can result in persistent employment issues. Indeed, this is reflected in the German data, which reported that 4% of individuals with TED had been forced to retire prematurely.<sup>28</sup> Overall, indirect costs attributable to sick leave and work disability in patients with TED ranged from €3,300 to €6,700 per person per year (Figure 3).<sup>28</sup> These data accord with interim results from the French VST disease burden survey of 103 patients with TED. Overall, 20% of patients had to professionally retrain, 17% lost their jobs, and 16% required leave from work for more than a year.<sup>32</sup>

The German data also reveal that, when compared with other conditions, TED confers a greater degree of work disability than thyroid conditions without eye involvement, non-thyroid autoimmune disease, benign nodular goiter, and polyendocrinopathy<sup>28,39</sup> and has higher total indirect costs compared with them all except other autoimmune diseases (Figure 3).<sup>28,39</sup>

A Danish study that used national registry data from 1994 to 2011 to assess productivity losses relating to thyroid diseases (n=862 patients,

including individuals with non-toxic goiter and hyperthyroidism) reported that patients with TED (n=76) had the most negative outcomes.<sup>40</sup> These included a 7-fold increased risk versus the general population of long-term sickness absence in the first year after diagnosis (twice the risk in subsequent years) and half the probability of returning to work after sickness absence or unemployment.<sup>40</sup>

**Figure 3. Work disability and total indirect costs associated with TED and other conditions; data from a German multidisciplinary center<sup>28,39</sup>**



HCA, human capital approach; FCA, friction cost approach; TED, thyroid eye disease

Work impairment and QOL are closely linked in patients with TED,<sup>28</sup> and individuals with prolonged periods of sick leave or disability are more likely to receive psychotherapy.<sup>41</sup> These findings emphasize the need for early, effective multidisciplinary treatment of TED to improve function and QOL and reduce associated indirect costs.<sup>41</sup> In terms of the most disabling symptoms of TED, significant associations have been reported between work disability and diplopia and optic neuropathy.<sup>28</sup> While optic neuropathy is a critical condition that is likely to be addressed quickly, diplopia is also disabling but less likely to be treated promptly, which may result in lost productivity and increased indirect costs.

Whether these cost data from Germany can be applied more broadly to other European healthcare systems is unclear, but they do provide an estimation of the indirect financial burden of TED and emphasize the public health relevance of the disease. Moreover, sick leave and work disability related to TED are likely to be similar across countries.

# What Are the Direct Costs of TED?

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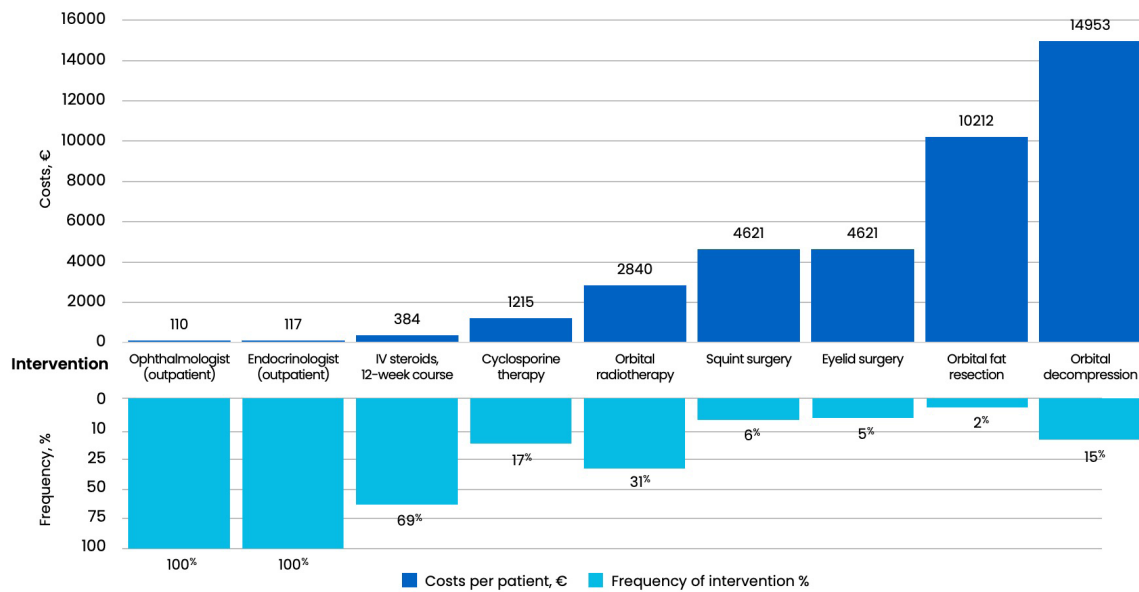
**PROF. DR KATHARINA PONTO:**

The hope is that new therapies for TED may reduce indirect costs by lowering rates of work impairment, decreasing disease complications, and reducing the incidence of compressive optic neuropathy. However, whether these benefits will be realized remains uncertain. It is also essential to consider that these treatments might lead to side effects, which could, in turn, generate additional indirect costs.

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Patients with moderate-severe TED often require long-term treatment and follow-up, likely resulting in substantial longitudinal direct costs, although data in this regard are scarce. An analysis of German healthcare data (n=310 patients) that linked ICD-10 codes with associated medical interventions and corresponding outpatient and inpatient costs revealed that the direct costs of TED were ~€400 per patient per year.<sup>28</sup> Direct costs were higher in patients with sight-threatening TED (~€1,200 per patient per year) than in patients with moderate-severe or mild TED (€370 and €330 per patient per year, respectively).<sup>28</sup> Surgery was one of the highest-cost interventions, particularly orbital decompression, but these treatments were used relatively infrequently compared with e.g. IV steroids (Figure 4). In the German health system, it appears that direct costs are lower than annual per patient indirect costs (see previous section).

**Figure 4. Direct costs associated with TED; data from a German multidisciplinary center<sup>28</sup>**



IV, intravenous

Drug expenditure data for biologics, including teprotumumab, in the treatment of TED are currently limited to the US<sup>42</sup> and clearly show high unit costs and associated monitoring and infusion costs. While expenditure is likely to be lower in Europe due to different pricing structures and healthcare systems, drug costs will still be substantially higher than with the current standard of care (IV steroids). It is hoped that more effective and targeted treatments will enable patients to avoid a severe disease trajectory, potentially leading to fewer long-term complications and a reduction in disability and the indirect costs associated with decreased work impairment. However, these expectations must be balanced against the possibility of side effects, which could contribute to functional impairment, work absenteeism, and the need for rehabilitation or additional interventions. The decision to use biologic treatments should involve a comprehensive discussion of the potential benefits and risks, considering both short-term and long-term impacts on the patient's health and QOL.

Future considerations of costs relating to biologic treatment of TED should include comparisons with other diseases. Recently published German data on neuromyelitis optica spectrum disorders (NMOSD) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) may be of relevance.<sup>43</sup> These autoimmune conditions are

treated with immunotherapies and may provide a case study for the potential direct costs and QOL improvements that may be seen as TED treatment evolves. Total annual costs per patient with NMOSD or MOGAD were €59,574; indirect costs represented 23% of this expenditure, while direct costs were primarily driven by immunotherapy and hospitalizations. Informal, unpaid assistance from family and caregivers accounted for 28% of total costs.<sup>43</sup> However, NMOSD and MOGAD are only partially comparable to TED, as there are no truly affordable alternatives to expensive immunomodulatory therapies for these conditions. In contrast, TED has less costly medical treatment options and surgical interventions available, making the cost dynamics distinct from those of NMOSD and MOGAD.

# How is TED Treated Currently?

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**PROF. DR GEORGE KAHALY:**

We are currently at about 6 or 7 out of 10 in terms of the effectiveness of available treatments for TED – there is certainly room to optimize as steroids are not disease-specific therapies.

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Treatment of TED should be tailored to its signs and symptoms (Table 1) with a focus on normalizing thyroid dysfunction, reducing inflammation, improving diplopia and proptosis (if present), and optimizing QOL. Aligned with EUGOGO recommendations,<sup>5</sup> within European multidisciplinary centers, patients with moderate-severe active TED with inflammatory signs receive treatment initiation with IV steroids, which are used at a higher dose in the presence of severe disease. The antiproliferative agent mycophenolate can be combined with IV steroids to stabilize the disease, and orbital radiotherapy is recommended in patients with restricted eye motility. Some TED specialists may use off-label biologics first-line in patients without inflammation but with diplopia or proptosis based on their expert clinical judgement. In some European health systems, tocilizumab and rituximab (recommended second-line in moderate-severe TED that is steroid resistant) require reimbursement, which can be a hurdle to their timely use. Moreover, even in specialist centers that treat TED, experience with tocilizumab is limited and assistance from a rheumatologist may be necessary during treatment initiation.

**Table 1. TED treatment landscape based on EUGOGO guidelines<sup>5</sup>**

| Phase           | Severity  |   |  |
|-----------------|---|---|--|
|                 | Mild  | Moderate-severe   | Sight threatening  |
| <b>Active</b>   | <ul style="list-style-type: none"> <li>Local measures</li> <li>Selenium supplementation</li> <li>Oral steroids if progressive disease or decreased QOL</li> </ul> | <ul style="list-style-type: none"> <li>IV steroids (+ MMF)</li> <li>Rituximab, tocilizumab, (teprotumumab*)</li> <li>Orbital radiation (+steroids)</li> </ul> | <ul style="list-style-type: none"> <li>IV steroid + urgent orbital decompression surgery</li> </ul>  |
| <b>Inactive</b> | <ul style="list-style-type: none"> <li>Rehabilitative surgery if impact of disease on QOL outweighs risks</li> </ul>  | <ul style="list-style-type: none"> <li>Rehabilitative surgery (as needed)</li> </ul>  | <ul style="list-style-type: none"> <li>IV steroids + urgent orbital decompression surgery</li> </ul> |

\*Limited availability in Europe. IV, intravenous; MMF, mycophenolate mofetil; QOL, quality of life; TED, thyroid eye disease

ATA / ETA survey data from 2021 reveal that IV steroids remain the first-line choice of treatment for moderate-severe TED among European clinicians. In the US, where teprotumumab was approved for the treatment of TED in 2020, ~40% of survey respondents reported using the anti-IGF-1R antibody first-line.<sup>44</sup>

Beyond expert care, initial treatment of moderate-severe TED is usually based on the options available to the clinician. For healthcare practitioners without TED expertise, this likely means local and lifestyle measures (lubricant eye drops, smoking cessation advice), oral steroids or watchful monitoring in selected patients, as recommended in the ATA / ETA consensus statement<sup>45</sup> based on apparent spontaneous resolution of TED symptoms in patients receiving placebo in randomized controlled trials. Failure to treat patients with moderate-severe disease does not reflect the evolving understanding of the subclinical effects of TED and likely results from an absence of clear referral pathways, lack of knowledge regarding available therapies, or wariness about their potential side effects. With a 12- to 24-month window for early intervention in patients with active TED, this opportunity may be lost in the absence of collaboration and communication between healthcare providers with and without TED expertise.

Data from the recently published PREGO III study reflect (and indeed include) the clinical experience of the faculty members.<sup>46</sup> Patients are now referred to EUGOGO centers more quickly and with less severe disease than a decade ago but are likely to have received steroids or

selenium elsewhere and may be relapsed or refractory to treatment. While these data indicate that awareness of TED is increasing in general practice, they also highlight a significant challenge for specialists. Many of these patients cannot receive or do not respond to more steroids, limiting options for later lines of therapy to off-label biologics, although these may not always be well tolerated. More treatment options and more precise guidance around managing relapsed or refractory patients are needed.



#### EMMA'S PATIENT EXPERT PERSPECTIVE:

Personally, I was treated with steroids, radiotherapy and, finally, decompression surgery. Of course, I am very interested in new drugs and new treatment paths that could deal with this disease in a different way. My steroid treatment at the onset of TED resulted in me developing osteoporosis and I wonder if this side effect occurs often in patients with TED.

The efficacy and safety of medications currently available in Europe for the treatment of TED have been reviewed,<sup>45,47</sup> concluding that IV steroids remain a logical first-line choice as they are globally available, low cost, and do not result in severe side effects when administered by experienced clinicians in specialist centers. While large cumulative doses of IV steroids may result in liver toxicity, provided patients are carefully screened for cardiovascular morbidities, hypertension, and unstable diabetes, their use remains appropriate.<sup>5,45</sup> The effect of oral and IV steroids in patients with TED has been compared prospectively with follow-up of 6 months.<sup>48</sup> Transient administration of IV steroids in specialist centers does not decrease bone mineral density, although this is observed with oral steroids. Patients who are given oral steroids for TED should also receive calcium, vitamin D, and potentially bisphosphonates, to prevent osteoporosis and bone loss.<sup>49</sup>

TED is predominantly treated by ophthalmologists in the US and UK, whereas in mainland Europe, patient care is evenly split between endocrinologists and ophthalmologists. This approach has practical advantages as it permits each specialist to work optimally within their own area of expertise and allows the most appropriate treatments and doses to be given at initiation with highly skilled management of side effects.

Even with proficient multidisciplinary care, it should be acknowledged that the current treatment of TED is not optimal (Table 2) as it relies on non-specific medications that address only some of its symptoms, e.g., steroids reduce CAS but do not fully resolve proptosis or motility issues, and radiotherapy can help address diplopia but not other sequelae. Off-label, second-line treatments such as tocilizumab and rituximab lack large, randomized trials to support their efficacy, further delineate their safety profiles, and justify their cost in patients with TED. Bearing in mind the heterogeneity of TED, finding a treatment that addresses all of its possible manifestations is likely to be challenging, but medications that are targeted to the disease mechanism may be more successful in this regard. The advent of new therapies for TED will necessitate treatment within specialist centers for appropriate administration and management of drug-related adverse events. Ultimately, early identification and treatment of TED is the best way to optimize outcomes, and this relies on increased awareness of the condition and better communication between general and specialist practices for rapid referral.

**Table 2. Strengths and weaknesses of current TED treatments**

| Treatment                         | Strengths  | Weaknesses  |
|-----------------------------------|--|---|
| <b>Steroids (oral, IV)</b>        | <ul style="list-style-type: none"> <li>• &gt;70 years of clinical experience<sup>47</sup></li> <li>• Global availability<sup>45</sup></li> <li>• Low / very low drug costs<sup>45</sup></li> <li>• Various formulations and doses<sup>5</sup></li> <li>• Rapid onset and strong effect on inflammatory components of TED<sup>45</sup></li> <li>• Rapid improvement of clinical symptoms<sup>45</sup></li> <li>• Beneficial effect on tissue swelling, visual acuity, and ocular motility<sup>47</sup></li> <li>• Improve QOL<sup>45</sup></li> </ul> | <ul style="list-style-type: none"> <li>• Provide symptomatic improvement only<sup>47</sup></li> <li>• Do not target TSHR or IGF-1R<sup>45</sup></li> <li>• Low / moderate effect on diplopia and proptosis<sup>45</sup></li> <li>• General precipitation of depression<sup>45,47</sup></li> <li>• Difficulty in sleeping<sup>47</sup></li> <li>• Potential weight gain<sup>45,47</sup></li> </ul> |
| <b>(Steroids +) mycophenolate</b> | <ul style="list-style-type: none"> <li>• RCT evidence showing superior treatment response vs IV steroids alone<sup>50</sup></li> <li>• RCT evidence of long-term efficacy and safety<sup>50</sup></li> </ul>   | <ul style="list-style-type: none"> <li>• Low / moderate effect on diplopia and proptosis<sup>50,51</sup></li> <li>• Do not target TSHR or IGF-1R<sup>5,51</sup></li> </ul>  |

| Treatment                            | Strengths   | Weaknesses  |
|--------------------------------------|---|---|
| <b>(Steroids +)<br/>radiotherapy</b> | <ul style="list-style-type: none"> <li>• RCT evidence of effect on motility in active TED<sup>52,53</sup></li> <li>• Additive anti-inflammatory and inactivating effect in combination with steroids<sup>5</sup></li> </ul> | <ul style="list-style-type: none"> <li>• No effect on proptosis<sup>45</sup></li> <li>• Caution required in patients with diabetic retinopathy or severe hypertension<sup>5</sup></li> </ul>  |
| <b>Tocilizumab</b>                   | <ul style="list-style-type: none"> <li>• Reduction in IL-6 induced inflammation<sup>5</sup></li> </ul>  | <ul style="list-style-type: none"> <li>• Single RCT in steroid-resistant TED showing improvement in CAS<sup>5,54</sup></li> <li>• Further studies needed<sup>47</sup></li> </ul>  |
| <b>Rituximab</b>                     | <ul style="list-style-type: none"> <li>• RCT evidence of CAS reductions vs IV steroids<sup>55</sup></li> </ul>  | <ul style="list-style-type: none"> <li>• Efficacy not definitely proven<sup>45,47</sup></li> <li>• No effect on proptosis or diplopia<sup>45</sup></li> <li>• Expensive<sup>45</sup></li> <li>• Linked to cytokine release syndrome<sup>47,56</sup></li> <li>• Not recommended in patients at risk for DON<sup>47,56</sup></li> </ul> |

CAS, clinical activity score; DON, dysthyroid optic neuropathy; IGF-1R, insulin-like growth factor-1 receptor; IL, interleukin; IV, intravenous; RCT, randomized controlled trial; TED, thyroid eye disease; TSHR, thyroid stimulating hormone receptor

# How Can Care for Patients With TED Be Improved?

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## EMMA'S PATIENT EXPERT PERSPECTIVE:

It is important that patients with TED are seen by multidisciplinary teams including endocrinologists and ophthalmologists, but also psychologists. Above all, TED should be treated by specialists from its onset; not all patients are referred to multidisciplinary centers in time and their symptoms worsen and become difficult to treat.

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## PROF. DR GEORGE KAHALY:

The delay of referral is a major issue. The results of treatment are always better if patients are referred earlier.

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Despite PREGO III data indicating that time from diagnosis to specialist referral is becoming shorter,<sup>46</sup> delay of referral for patients with active disease is still a problem. Treatment outcomes are better when patients are seen by experts earlier, but a tendency remains for general practitioners and ophthalmologists / endocrinologists without TED expertise to administer local measures and oral steroids, waiting up to a year before referral. During this period, patients can become demoralized, struggle with symptoms, and may even stop pursuing treatment. This issue is best tackled by the creation of care networks, educational initiatives, collaboration between general practice and TED experts, and clear communication of an open-door policy for rapid referrals. Owing to the complexity of TED, management by experts is optimal; conveying this diplomatically to clinical peers is a vital step in improving disease outcomes.

Educating patients with Graves' disease about their potential to develop TED should be prioritized. Approximately 40% of patients with Graves' disease will develop ocular manifestations<sup>2</sup> and open dialogue between patients with Graves' disease and their clinician(s) is vital to ensure that any eye changes are communicated quickly and can be managed or referred on as necessary. Importantly, when patients with

TED are referred for specialist consultation, the medical and surgical options should be fully explained to them, including potential outcomes and how long the multi-step treatment could last. This approach will allow them to make informed decisions and remain adherent and involved with their own treatment, while reducing associated anxiety. Careful consideration should be given to the language used in these situations; for example, use of the word 'normalized' may introduce unrealistic expectations related to regaining their original appearance. Patients may also derive reassurance from their interactions with other patients with TED, who are also undergoing or have undergone treatment, whether through patient associations or through interactions at specialist treatment centers.



**DR MARIO SALVI:**

Patients with Graves' disease and their doctors must talk to each other – patients must be quick to alert their physicians if there are changes in their eyes. TED can then be treated early with success.

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**EMMA'S PATIENT EXPERT PERSPECTIVE:**

TED patients can be difficult as they become discouraged over time – often they have not been made aware of what they will face. They can become pessimistic and may get confused between Graves' disease and TED. Patient advocacy groups and clinicians must work together, educate patients about the disease, and tell them what they can expect, both the negative and positive aspects. Patients may still be worried but they will be more prepared and aware.

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The UK TED Amsterdam Declaration Group (TEAMeD) was set up to implement the 2009 Amsterdam Declaration<sup>57</sup> by raising awareness of TED among endocrinologists and patients with Graves' disease, calling for preventive measures as well as faster diagnosis and referral of TED to improve outcomes. The TEAMeD-5 program initiated in 2017 brings together relevant societies to educate and provide materials about TED and improve service provision across the UK.<sup>58</sup> Similar programs could be initiated in other European countries where awareness and rates of specialist referrals for TED remain low, including the development of directories of centers of excellence and specialists for use by clinicians

and patients. Identifying multidisciplinary centers could help to avoid unnecessary / inappropriate treatment, reduce time to effective treatment, and minimize loss of patients from the care pathway. Of note, the EUGOGO website hosts an interactive map of TED specialist sites in Europe (<https://www.eugogo.eu/en/where-we-are/>).

Media involvement to raise awareness of TED and the need for appropriate specialist treatment would be welcome, as would the development of a best practice portal for clinicians and patient organizations. Patient organizations and advocates have a vital role in disseminating correct information and identifying patients who should receive rapid referral to centers with TED expertise or who may need additional psychological support.



#### **EMMA'S PATIENT EXPERT PERSPECTIVE:**

A problem met by our association concerns ophthalmologists, who sometimes are not aware of TED, confusing it at the beginning with other disorders or not distinguishing between Graves' disease and TED. Therefore, it seems appropriate to provide more information to ophthalmologists, not only those in specialized centers, but also normal professionals.

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## Improving Care For Patients With TED

Role of:

### ENDOCRINOLOGISTS

- Remain vigilant for eye changes in patients with Graves' disease and ensure open dialogue with these patients
- Consult with a TED-expert ophthalmologist if: TED diagnosis is uncertain; in cases of moderate-severe or sight-threatening TED; or if surgery may be required

### OPHTHALMOLOGISTS

- Consult with a TED-expert endocrinologist if an underlying thyroid issue is suspected and the diagnosis of TED is uncertain
- Carefully evaluate any sign of visual deterioration and discomfort over time – mandatory for disease progression assessment

### ALL HEALTHCARE PROFESSIONALS

- Be aware of the signs, symptoms, and methods of diagnostic assessment of TED
- Familiarize yourself with the closest multidisciplinary center / TED specialists
- Ensure rapid referral to multidisciplinary care
- Include psychologists in TED treatment where possible
- Explain potential outcomes and duration of multi-step treatment to patients

# What Does the Future Look Like For Patients With TED?

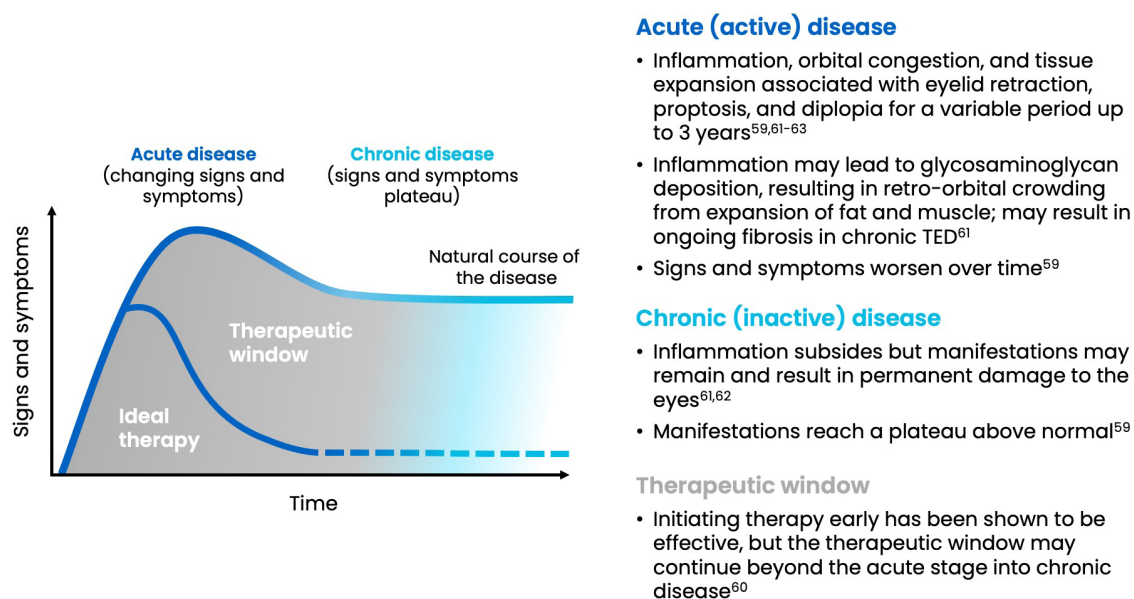


## MR JIMMY UDDIN:

TED is entering a golden era – in terms of understanding the disease and improving treatment options.

The perception of how to treat TED is evolving. It is now thought that the medical therapeutic window extends beyond the acute inflammatory phase of Rundle's curve into the chronic phase, once manifestations have seemingly plateaued (Figure 5). The multifaceted nature of TED means that an increasing number of documented phenotypes fall outside the original disease course paradigm.

**Figure 5. Natural history of TED<sup>59-63</sup>**



Evolving understanding of the pathogenesis of TED indicates that underlying biochemical changes, such as increased expression of

IGF-1R, occurs in both the active and nominally inactive phases of the disease (albeit at lower levels in the inactive versus active phase).<sup>64</sup> Increased scientific and translational research regarding TED has allowed development of targeted therapies (Figure 6) and raised hope for improved outcomes.

**Figure 6. Potential novel targeted therapies for TED, currently being tested in various clinical trials<sup>65-68</sup>**



Veligrotug: NCT06021054; NCT05176639; linsitinib: NCT06112340; NCT05276063; lonigutamab: NCT05683496; KI-70: NCT02904330; tocilizumab: NCT04876534; NCT01297699; satralizumab: NCT06106828; NCT05987423; LASN-01: NCT06226545; NCT05331300; batoclimab: NCT05524571; NCT05517421; NCT05517447; efgartigimod: NCT06307626; NCT06307613

Pre-treated patients with chronic TED with low disease activity have received teprotumumab in a post-FDA approval, Phase IV study, demonstrating moderate regression of proptosis versus placebo from Week 12.<sup>69</sup> Moreover, a recent US study has reported that teprotumumab contributed to a significant decrease in the number of orbital decompression surgeries performed at a tertiary academic center since 2020. Over the same period, admissions to this facility for TED increased steadily despite the COVID-19 pandemic.<sup>70</sup> The durability of these outcomes requires further study as does the potential for difference in response and need for surgery with teprotumumab in patients with chronic versus active disease.



**PROF. DIEGO STRIANESE:**

The definition of mild TED with minimal symptoms should be revised. The global labor market is undergoing profound changes driven by technological progress and economic shifts. Workforce transformations precipitated by the COVID-19 crisis and new media have fundamentally reshaped the employment landscape. Many patients rely on their face and appearance at work, meaning that individuals with what we consider 'mild disease', including minimal lid retraction, are asking for rapid, effective solutions. They don't think that their condition is mild. We are seeing a change in the types of patients who need and want treatment.

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With new drugs comes increased industry involvement in the study and treatment of TED; it is imperative that recognized TED experts interact with pharmaceutical companies to develop clinical trials that reflect real-world patient scenarios. Moreover, with clinical trials actively recruiting from the limited pool of TED patients, it is more important than ever that clinicians, including those in private practice, are made aware of recommended treatments, referral pathways, and the importance of collaboration. Most trials will exclude patients who have undergone surgery for TED and so it is vital that clinicians adhere to guidance to initiate treatment with medical therapies and consider clinical trials before moving on to more invasive treatments.



**DR MARTA PÉREZ LÓPEZ:**

Now that new treatments for TED are coming, we need to be mindful of their secondary effects – these sorts of treatments should be given in referral centers otherwise these strategies may not be used properly.

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While significant challenges remain, the treatment and understanding of TED is transforming rapidly. The last 5 years have seen a shift in the therapeutic landscape and these changes will continue with ongoing investigation of potential medications and the growing awareness and necessity of multidisciplinary centers specializing in TED. Patients should be offered the opportunity to participate in clinical trials and be given practical information about where and how to enroll.



#### EMMA'S PATIENT EXPERT PERSPECTIVE:

We are entering a new period for TED treatment; never before have so many studies been conducted and new drugs been in development. Several new treatments are underway and a greater understanding and heightened interest in the pathology of TED suggests a positive future for patients. I think we can be very optimistic. The situation is really encouraging, and I am full of hope for the future.

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# Conclusions

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The expert roundtable discussions captured herein emphasize the substantial psychosocial and socioeconomic burden of TED, alongside the relative paucity of published data in this regard.

TED should no longer be considered a purely cosmetic condition, but rather a disease that imparts both visual and physical limitations that can impede patients' daily activities and ability to work.

Beyond TED specialists and patient advocates and associations, awareness and understanding of TED remain limited, resulting in delayed or under-diagnosis and inappropriate treatment.

Education about TED is vital to improve patient outcomes, as is increased communication between TED-expert and non-expert physicians. Collaboration in this way could ensure timely treatment, preferably in a multidisciplinary setting, including psychological support.

Media involvement to raise awareness of TED and the need for appropriate specialist treatment would be welcome, as would the development of a best practice portal, highlighting multidisciplinary centers and TED specialist networks.

Despite current challenges, including non-specific treatments and low disease awareness, the future looks bright for patients with TED, with increased focus on delineating its underlying pathophysiology and developing targeted treatments.

# Roundtable Faculty

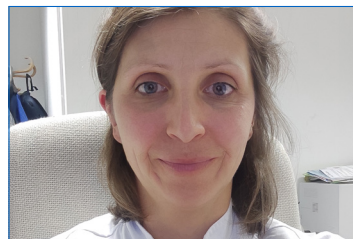
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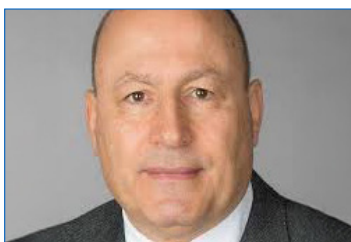
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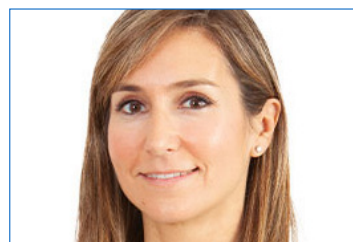
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**2. Co-chair: Mr Jimmy Uddin**

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Founder and Past President of the Italian Association of Basedow and Thyroid Patients (AIBAT)

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# References

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1. Pokhrel B, Bhusal K. Graves disease. StatPearls Publishing 2023. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK448195/> (accessed December 2024)
2. Chin YH, et al. Prevalence of thyroid eye disease in Graves' disease: A meta-analysis and systematic review. *Clin Endocrinol* 2020;93:363-374
3. Bartley GB, et al. Clinical features of Graves' ophthalmopathy in an incidence cohort. *Am J Ophthalmol* 1996;121:284-290
4. Smith TJ, Hegedüs L. Graves' disease. *N Engl J Med* 2016;375:1552-1565
5. Bartalena L, et al. The 2021 European Group on Graves' Orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves; orbitopathy. *Eur J Endocrinol* 2021;185:G43-G67
6. Kahaly GJ, et al. 2018 European Thyroid Association guideline for the management of Graves' hyperthyroidism. *Eur Thyroid J* 2018;7:167-186
7. Smith TJ, Janssen JAMJL. Insulin-like growth factor-1 receptor and thyroid associated ophthalmopathy. *Endocr Rev* 2019;40:236-267
8. Adams TE, et al. Structure and function of the type 1 insulin-like growth factor receptor. *Cell Mol Sci* 2000;57:1050-1093
9. Kossler AL, et al. Teprotumumab and the evolving therapeutic landscape in thyroid eye disease. *J Endocrinol Metab* 2022;107:S36-S46
10. Girnita L, et al. It takes two to tango: IGF-1 and TSH receptors in thyroid eye disease. *J Clin Endocrinol Metab* 2022;107(Suppl 1): S1-S12
11. Krieger CC, et al. Bidirectional TSH and IGF-1 receptor cross talk mediates stimulation of hyaluronan secretion by Graves' disease immunoglobulins. *J Clin Endocrinol Metab* 2015;100:1071-1077
12. Tsui S, et al. Evidence for an association between thyroid stimulating hormone and insulin-like growth factor-1 receptors: a tale of two antigens implicated in Graves' disease. *J Immunol* 2008;181:4397-4405
13. Perros P, et al. Graves' orbitopathy as a rare disease in Europe: a European Group on Graves' Orbitopathy (EUGOGO) position statement. *Orphanet J Rare Dis* 2017;12:72
14. Terwee CB, et al. Long-term effects of Graves' ophthalmopathy on health-related quality of life. *Eur J Endocrinol* 2002;146:751-757
15. Shah SS, Patel BC. Thyroid eye disease. StatPearls Publishing 2023. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK582134/> (Accessed December 2024)
16. Szelog J, et al. Thyroid eye disease. *Missouri Med* 2022;119:343-350
17. Strianese D, et al. Unilateral proptosis in thyroid eye disease with subsequent contralateral involvement: retrospective follow-up study. *BMC Ophthalmol* 2013;13:21
18. Croker EE, et al. Thyroid disease: using diagnostic tools effectively. *Aust J Gen Pract* 2021;50:16-21
19. Eckstein AK, et al. Thyrotropin receptor autoantibodies are independent risk factors for Graves' ophthalmology and help to predict severity and outcome of disease. *J Clin Endocrinol Metab* 2006;91:3464-3470
20. Kahaly GJ, et al. Thyroid stimulating antibodies are highly prevalent in Hashimoto's thyroiditis and associated orbitopathy. *J Clin Endocrinol Metab* 2016;101:1998-2204

21. Kahaly GJ, et al. High titers of thyrotropin receptor antibodies are associated with orbitopathy in patients with Graves disease. *J Clin Endocrinol Metab* 2019;104:2561-2568
22. Kahaly GJ, et al. TSH receptor antibodies: relevance and utility. *Endor Pract* 2020;26:97-106
23. Eckstein AK, et al. Euthyroid and primarily hypothyroid patients develop milder and significantly more asymmetrical Graves ophthalmopathy. *Br J Ophthalmol* 2009;93:1052-1056
24. Boddu N, et al. Not all orbitopathy is Graves': discussion of cases and review of literature. *Front Endocrinol* 2017;8:184
25. Uddin J, et al. Phenotypes of thyroid eye disease. *Ophthalmic Plast Reconstr Surg* 2018;34:S28-S33
26. Delfino LC, et al. Related quality of life questionnaire specific to dysthyroid ophthalmology evaluated in a population of patients with Graves' disease. *Arch Endocrinol Metab* 2017;61:374-381
27. Kahaly GJ, et al. Psychosocial morbidity of Graves' orbitopathy. *Clin Endocrinol* 2005;63:395-402
28. Ponto KA, et al. Public health relevance of Graves' orbitopathy. *J Clin Endocrinol Metab* 2013;98:145-152
29. Kahaly GJ, et al. Psychosocial factors in subjects with thyroid-associated ophthalmopathy. *Thyroid* 2002;12:237-239
30. Yeatts RP. Quality of life in patients with Graves ophthalmopathy. *Trans Am Ophthalmol Soc* 2005;103:368-411
31. Ferløv-Schwensen C, et al. Death by suicide in Graves' disease and Graves' orbitopathy: a nationwide Danish Register study. *Thyroid* 2017;27:1475-1480
32. Bartès B, on behalf of the French patient organization "Vivre Sans Thyroid" (Living Without Thyroid). 'The patients' point of view'. Part of the 'Crossed perspectives on the management and burden of Graves' ophthalmopathy' conference debate. Presented at the 40th Congress of the French Society of Endocrinology (SFE); 16-18 October, 2024, Clermont-Ferrand, France
33. Fayers T, Dolman PJ. Validity and reliability of the TED-QOL: a new three-item questionnaire to assess quality of life in thyroid disease. *Br J Ophthalmol* 2011;95:1670-1674
34. Terwee CB, et al. Development of a disease specific quality of life questionnaire for patients with Graves' ophthalmopathy: the GO-QOL. *Br J Ophthalmol* 1998;82:773-779
35. Sharma A, et al. Measuring health-related quality of life in thyroid eye disease. *J Clin Endocrinol Metab* 2022;107:S27-S35
36. Wickwar S, et al. What are the psychosocial outcomes of treatment for thyroid eye disease? A systematic review. *Thyroid* 2014;24:1407-1418
37. Braun TL, et al. Orbital decompression for thyroid eye disease. *Semin Plast Surg* 2017;31:40-45
38. Cockerham KP, et al. Quality of life in patients with chronic thyroid eye disease in the United States. *Ophthalmol Ther* 2021;10:975-987
39. Radermacher LK, et al. Type I diabetes is the main cost driver in autoimmune polyendocrinopathy. *J Clin Endocrinol Metab* 2020;105:e1307-e1315
40. Nexo MA, et al. Increased risk of long-term sickness absence, lower rate of return to work, and higher risk of unemployment and disability pensioning for thyroid patients: a Danish register-based cohort study. *J Clin Endocrinol Metab* 2014;99:3184-3192
41. Ponto KA, et al. Quality of life and occupational disability in endocrine orbitopathy. *Dtsch Arztebl Int* 2009;106:283-289
42. Shah SA, et al. Comparison of treatment cost and quality-of-life impact of thyroid eye disease therapies. *Invest Ophthalmol Vis Sci* 2022;63:A0344

43. Hümmer MW, et al. Costs and health-related quality of life in patients with NMO spectrum disorders and MOG antibody-associated disease. *Neurology* 2022;98:e1184-e1196
44. Brito JP, et al. A survey of the management of thyroid eye disease among American and European Thyroid Association members. *Thyroid* 2022;32:1535-1546
45. Burch HB, et al. Management of thyroid eye disease: a consensus statement by the American Thyroid Association and the European Thyroid Association. *Thyroid* 2022;32:1439-1470
46. Schuh A, et al. Presentation of Graves' orbitopathy within European Group on Graves' Orbitopathy (EUGOGO) centres from 2012 to 2019 (PREGO III). *Br J Ophthalmol* 2024;108:294-300
47. Wolf J, et al. Drug safety in thyroid eye disease – a systematic review. *Expert Opin Drug Saf* 2022;21:881-912
48. Kahaly GJ, et al. Randomized, single blind trial of intravenous versus oral steroid monotherapy in Graves' orbitopathy. *J Clin Endocrinol Metab* 2005;90:5234-5240
49. Yang DD, et al. Medical management of thyroid eye disease. *Saudi J Ophthalmol* 2011;25:3-13
50. Kahaly GJ, et al. Mycophenolate plus methylprednisolone versus methylprednisolone alone in active, moderate-to-severe Graves' orbitopathy (MINGO): a randomised, observer-masked, multicentre trial. *Lancet Diabetes Endocrinol* 2018;6:287-298
51. Taylor PN, et al. New insights into the pathogenesis and nonsurgical management of Graves orbitopathy. *Nat Rev Endocrinol* 2020;16:104-116
52. Mourits MP, et al. Radiotherapy for Graves' orbitopathy: randomised placebo-controlled study. *Lancet* 2000;355:1505-1509
53. Prummel MF, et al. A randomized controlled trial of orbital radiotherapy versus sham irradiation in patients with mild Graves' ophthalmopathy. *J Clin Endocrinol Metab* 2004;89:15-20
54. Perez-Moreiras JV, et al. Efficacy of tocilizumab in patients with moderate-to-severe corticosteroid-resistant Graves' orbitopathy: a randomized clinical trial. *Am J Ophthalmol* 2018;195:181-190
55. Salvi M, et al. Efficacy of B-cell targeted therapy with rituximab in patients with active moderate to severe Graves' orbitopathy: a randomized controlled study. *J Clin Endocrinol Metab* 2015;100:422-431
56. Vannucchi G, et al. Efficacy profile and safety implications of very low dose rituximab in patients with Graves' orbitopathy. *Thyroid* 2021;31:821-828
57. Amsterdam Declaration. Graves' orbitopathy: improving outcomes for thyroid eye disease – The Amsterdam Declaration. *Thyroid* 2010;20:351-352
58. Taylor P, et al. Improving outcomes in thyroid eye disease. *The Endocrinologist* 2019;131. Available at: <https://www.endocrinology.org/endocrinologist/131-spring19/opinion/improving-outcomes-in-thyroid-eye-disease/#:~:text=The%20Amsterdam%20Declaration%2C%20an%20international%20declaration%20signed%20in,to%20diagnosis%20and%20referral%20to%20a%20specialist%20centre> (accessed December 2024)
59. Wang Y, et al. Thyroid eye disease: how a novel therapy may change the treatment paradigm. *Ther Clin Risk Manag* 2019;15:1305-1318
60. Ugradar S, et al. Teprotumumab for the treatment of thyroid eye disease. *Endocr Rev* 2024;45:843-857
61. Bhatti MT, Dutton JJ. Thyroid eye disease: therapy in the active phase. *J Neuro Ophthalmol* 2014;34:186-197
62. Bothun ED, et al. Update on thyroid eye disease and management. *Clin Ophthalmol* 2009;3:543-551
63. Bartalena L, et al. Management of Graves' ophthalmopathy: reality and perspectives. *Endocr Rev* 2000;21:168-199

64. Ugradar S, et al. Teprotumumab for non-inflammatory thyroid eye disease (TED); evidence for increased IGF-1R expression. *Eye* 2021;35:2607–2612
65. Marcinkowski P, et al. A new highly thyrotropin receptor-selective small molecule antagonist with potential for the treatment of Graves' orbitopathy. *Thyroid* 2019;29:111–123
66. Park JW, Yoon JS. A review of novel medical treatments for thyroid eye disease. *Korean J Ophthalmol* 2024;38:249–259
67. TEPEZZA (teprotumumab-trbw). Package insert: Horizon Therapeutics, July 2023. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2023/761143s023lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761143s023lbl.pdf) (Accessed December 2024)
68. Amgen Press Release; Apr 2024. Amgen to submit teprotumumab marketing authorization application to the European Medicines Agency. Available at: <https://www.prnewswire.com/news-releases/amgen-to-submit-teprotumumab-marketing-authorization-application-to-the-european-medicines-agency-302128358.html> (accessed December 2024)
69. Douglas RS, et al. Efficacy and safety of teprotumumab in patients with thyroid eye disease of long duration and low disease activity. *J Clin Endocr Metab* 2024;109:25–35
70. Topilow NJ, et al. Orbital decompression following treatment with teprotumumab for thyroid eye disease. *Can J Ophthalmol* 2025;60:e59–e64