I'm not a bot

Management goals include maintenance of general health and well-being, achieving a euthyroid state (without post-treatment hypothyroidism), and promotion of smoking cessation. Both smoking cessation and euthyroidism help prevent further exacerbation and decrease the duration of active disease. From an ophthalmologist's perspective, the primary goal is to preserve visual function, while also preventing exposure keratopathy, correcting diplopia, and improving blink dynamics and cosmesis. Smoking cessation is a key part of treatment. Cigarette smoking Increases severity of disease Decreases the effectiveness of core treatment methods [3] Cyanide, contained in cigarette smoke, is converted in the body to thiocyanate, an anti-thyroid agent inhibits iodine uptake increases iodine excretion inhibits thyroid hormone synthesis Smokers are twice as likely to develop Graves' disease when compared to nonsmokers. Patients with Graves' disease who smoke are 7.7 times more likely to develop TED when compared to nonsmokers. Smoking reduces the effectiveness of TED treatments such as corticosteroids and RAI. TED is a self-limiting disease, with patients moving from the active to quiescent phase within 1-3 years with a 5-10% risk of recurrence [10]. Treatment for TED should start at the time of the diagnosis, as treatment becomes less effective as the disease progresses from the early, acute, active phase to the chronic quiescent phase. Rundle's Curve (Figure 22) Early initiation of therapy is crucial in diminishing the final severity of disease manifestations. Treatment initiation Treatment initiated during the early months of the active inflammatory phase has been shown to be most effective. Initiation of therapy during the final months of active inflammatory phase has little effect on the final outcome of disease. Once the chronic fibrotic stage has set in, treatment options become more limited, i.e. primarily surgical. Figure 22: Rundle's curve. As seen in the representation of TED activity over time in the Rundle's curve, early initiation of therapy is crucial in diminishing the final severity of disease manifestations. The majority of patients with TED (~75%) have mild to moderate disease and require primarily supportive care as a means of symptom management. Ocular lubrication, by way of daytime eyedrops and nighttime ophthalmic ointment, is the mainstay of treatment for mild to moderate disease. Topical cyclosporine has been shown to be beneficial in reducing symptoms of ocular surface irritation [10]. The following lifestyle modifications are also helpful adjuncts to ocular lubrication Smoking cessation Sodium restriction to reduce water retention and tissue edema Sleeping with the head of the bed elevated to decrease orbital edema Sunglasses to decrease photophobia and feelings of dryness Oral NSAIDs can be used if periocular pain is a prominent complaint [10]. In the presence of diplopia, temporary press-on prism lenses (e.g. Fresnel) can be utilized. Once stability in diplopia is achieved, the prism can be ground into glasses. Alternatively, for stable diplopia, the patient may undergo strabismus surgery, assuming the patient has been in the stable phase of TED for several months. Mineral supplementation with selenium, when taken regularly, has been shown to exert a significant benefit in European patients with mild, non-inflammatory orbitopathy, but the benefit of this supplementation in other regions is debated [18]. Approximately 20% of patients with TED undergo some type of surgical intervention [19]. In one study, 13% of patients with TED had eyelid surgery, 9% strabismus surgery, and 7% orbital decompression [19]. As a general guideline, surgery is not advised until a euthyroid state is maintained and the TED has been in the stable phase for at least 6-9 months. Exceptions include visual loss from compressive optic neuropathy or corneal exposure, in which cases urgent surgical intervention is warranted. In order to prevent repeat surgery following recovery from subsequent procedures, surgery for TED occurs in the following order, whenever possible Orbital decompression Strabismus surgery Eyelid surgery Aside from threatening vision and causing ocular and orbital pain, TED can be disfiguring and emotionally and psychologically taxing for many patients. Waxing and waning symptoms can be frustrating for both patient and provider. Education and reassurance are integral components of patient care. Peer support groups are invaluable for many patients. The following section starts with an overview of managing hyperthyroidism, followed by the different treatment options used in TED. It concludes with a discussion about therapeutic modalities specific to each sign or symptom associated with TED. While the course of TED does not parallel the status of systemic thyroid disease, achieving a euthyroid state is an important part of management. Hyper- or hypothyroidism has been associated with a greater severity score than euthyroid patients. Restoration of a euthyroid state by antithyroid drugs has been associated with improvement of TED over several months [20]. Oral beta-blockers can be used for symptom control (Figure 23). They decrease conversion of free T4 to T3. They decrease heart rate, palpitations, anxiety, and heat intolerance. Propylthiouracil and methimazole, thiourea derivatives, are used for thyroid hormone suppression. Remission rates are 30-50% at 12-24 months [21]. Relapse and/or hypothyroidism can occur. Thyroidectomy can successfully treat the hyperthyroid state. Nearly half of patients will become hypothyroid following surgery so close monitoring is needed [21]. Many studies have shown that post-thyroidectomy hypothyroidism results in worsening progression of TED [22]. Consider thyroidectomy in patients who are high risk for severe exacerbations of hyperthyroidism and are refractory to other treatment modalities [10]. Smokers Severe, active TED Elevated T3 concentrations Radioactive Iodine (RAI) 80% of patients achieve a hypothyroid state at 6-12 months [21]. RAI therapy is known to exacerbate TED in nearly 1/3 of patients undergoing treatment [23]. This may be caused by an increased release of TSH-R antigens from the thyroid cells, which enhances the immune response [8]. Smokers are more likely to demonstrate worsening following RAI [24]. Closely monitor thyroid labs following RAI therapy . "Block and replace" therapy (RAI + methimazole + thyroxine) has been shown to limit post-RAI hypothyroidism [10]. RAI with moderate-dose oral prednisone is indicated when the risks of worsening TED outweigh the potential risks of systemic side effects from glucocorticoid therapy [22]. Thyroid Storm [22] This hypermetabolic state is triggered by release of excessive thyroid hormone, which can lead to severe hypotension, heart failure, and shock. It is inevitably fatal if untreated. Triggers include stress (i.e. surgery, anesthesia), thyroid surgery, or RAI. To prevent thyrotoxicosis, avoid operating on patients who are currently hyperthyroid. Figure 23: Anti-thyroid drug mechanisms. This diagram depicts the formation of thyroid hormone, as well as the mechanism of action of anti-thyroid drugs to decrease levels of circulating thyroid hormone. Overview of Treatment Options Corticosteroids are a mainstay of treatment in TED. The benefit derived from corticosteroid administration is due to anti-inflammatory and immunosuppressive effects. Unfortunately, a significant percentage of patients respond only partially (or not at all), and recurrences upon dose reduction or cessation are not infrequent [19]. Oral prednisone [19] This is typically started in high doses (60-100 mg daily). Most effective in treating soft tissue changes and optic neuropathy Usually tapered slowly over a course of several months Multiple studies show a mean effectiveness rate of ~ 60%. Drawbacks include High rate of ineffectiveness (~ 40%) Need for high doses for an extended period of time Frequent relapses upon dose reduction/therapy cessation Multiple potential side effects, including but not limited to Cushing's syndrome Weight gain Increased risk of infection Exacerbation of diabetes mellitus, hypertension, and/or osteoporosis Intravenous (IV) corticosteroids [15 ,25] Compared to oral administration, IV is usually better tolerated and more effective (mean effectiveness ~ 70%). Compared to months of treatment with oral prednisone, IV treatment usually lasts 12 weeks (6 weeks – 500 mg once weekly; 6 weeks – 250 mg once weekly), which allows for easy and early detection of "non-responders." IV decreases the need for additional medical therapy. Additional considerations If prolonged high-dose treatment is anticipated, treat with calcium, vitamin D, and a proton pump inhibitor (for patients at high risk for gastric ulceration). Incorporate frequent monitoring of serum electrolytes, blood glucose, liver function tests (LFTs), and blood pressure. Patients receiving cumulative doses exceeding 8 g are at risk for hepatic toxicity, electrolyte disturbances, and cardiac arrhythmias [25]. Orbital radiotherapy (ORT) has been used in the management of TED for nearly a century and can be used alone or in conjunction with corticosteroids [26 ,27]. Mechanisms of action [28] Lymphocytes are temporarily sterilized. Terminal differentiation in orbital fibroblasts is induced. Adipocyte differentiation and fatty hypertrophy are limited. This is more effective in patients < 40 years old who have more orbital fat hypertrophy. Radiation induces death of tissue-bound monocytes. Radiation blunts the immune response at the orbit, reducing inflammation of both the ocular surface and eyelids in ~ 60% of patients [10]. ORT has not been shown to have notable effects on proptosis or eyelid retraction. ORT can be used to treat the following sequelae of TED Compressive optic neuropathy Ocular surface and periorbital tissue inflammation Orbital congestion Strabismus and ocular motility deficits Treatment regimen and effects Use 2000 cGy, administered over 10 treatment sessions, during a 2-week time course [26]. A maximum effect occurs around 6 months post-treatment [29]. Treatment is associated with a transient exacerbation of periorbital edema, conjunctival injection, and chemosis [29]. The role of ORT monotherapy has been controversial due to highly irregular results [26]. Effectiveness rates range from 20% - 90% in previously published studies. The most convincing evidence for benefit is found in the treatment of restrictive vertical strabismus. A recent Cochrane review concluded that the combination of corticosteroids + ORT has a more sustained anti-inflammatory effect, leading to a decreased risk of compressive optic neuropathy in active TED patients, when compared to treatment with either corticosteroids or ORT monotherapy [27]. Contraindications [29] Patients with underlying microvascular retinopathy (e.g. diabetic or hypertensive retinopathy) have an increased incidence of radiation retinopathy (1-2%). Patients may have increased risk of cataracts. There is a theoretical concern for tumorigenesis, and thus, ORT is typically avoided in patients younger than 35 years. Selenium [18] When taken regularly for one year, selenium has been shown to exert significant benefits in patients with mild, non-inflammatory orbitopathy. One study showed a benefit from selenium supplementation (100 µg twice daily) in Europe where the soil was selenium deficient. The benefit of selenium supplementation from non-selenium-deficient populations is not known. Emerging Therapies Azathioprine [30] This is a chemotherapeutic agent that inhibits DNA synthesis. It is currently being studied in a Combined Immunosuppression and Radiotherapy in TED (CIRTED) trial [31]. Sporadic case reports have shown a benefit with use of the anti-TNF alpha biologics infliximab and etanercept. Rituximab [32] This targets CD-20 on B-cells, which leads to B-cell depletion in the thyroid gland and decreased TSI production. A recent study showed TED patients with CAS ≥ 4 that received rituximab (1000 mg, IV, twice over a two week interval) showed an average decrease in CAS that ranged from 2.3 to 4.7, with a median decrease ranging from 2.5 to 4.5. The overall efficacy of rituximab therapy is complicated by the variable presentations and course of TED. Teprotumumab This is a human monoclonal antibody (Graves' Disease IgG – GD-IgG) against the IGF-1-R recently investigated (phase II clinical trial) in patients with active, moderate to severe TED. IGF-1-R has mitogenic and anti-apoptotic functions. GD-IgG interacts directly with IGF-1-R. IGF-1-R is upregulated in TED. Anti-IGF-1-R therapy may interfere with this abnormal signaling pathway present in TED. Back Next last updated: 11/18/2016 Share this page: Chase A Liaboe, BA (M4), Brittany A. Simmons, MD*, Thomas J Clark, MD, Erin M Shriver, MD September 1, 2016; updated January 9, 2017; *updated January 17, 2020 Introduction Thyroid eye disease (TED) is an inflammatory disease of the eye and the surrounding tissues. The inflammation is due to an autoimmune reaction - the body's immune system is attacking tissues within and around the eye socket. TED is sometimes referred to by other names, such as Graves' ophthalmopathy, Graves' orbitopathy, thyroid-associated ophthalmopathy, and/or thyroid orbitopathy. About 90% of TED patients also have Graves' disease, an autoimmune disorder that causes excess thyroid hormone production (hyperthyroidism). However, 10% of patients with TED have either a normal-functioning or under-functioning thyroid (e.g. Hashimoto's thyroiditis). While control of systemic thyroid hormone levels is crucial in patients with TED, the ocular disease course and severity does not always correlate with thyroid hormone levels. Most patients with TED have signs and/or symptoms in both eyes, however the severity can differ between the eyes. Some of the most common manifestations of TED: Swelling in and around the eye socket Retraction (tightening) of the eyelids Strabismus (the eyes are not in alignment with each other) and diplopia (double vision) Dry, irritated, red eyes More severe ocular effects from TED are rare, but can occur and include vision loss from damage to the optic nerve and breakdown/infection of the cornea (the transparent, outermost layer of the eye that we see through). Figures 1 and 2. These patients have some of the classic signs and symptoms of TED. Note the swelling around the eye, retraction of the eyelid, and injection of the conjunctiva. Epidemiology TED is the most common cause of both orbital disease and exophthalmos (external protrusion of the eyeball from the socket) in North America and Europe. TED occurs more frequently in women than in men, with both sexes having two age ranges in which TED is most likely to be diagnosed. Females 16 per 100,000 (0.016%) females have TED Most diagnoses occur between 40-44 and 60-65 years old Males 3 per 100,000 (0.003%) males have TED Most diagnoses occur between 45-49 and 65-69 years old Risk factors for the development of TED include the following Age (see above age ranges) Sex (females more likely to be diagnosed with TED) Ethnicity (higher incidence among people of black and Asian/Pacific Island ethnicity) [1] Family history of TED or other thyroid disorders Smoking, or exposure to tobacco smoke Thyroid dysfunction (particularly hyperthyroid) [2] Presence of thyroid stimulating hormone receptor antibodies/thyroid stimulating immunoglobulin [3] Radioactive iodine therapy [4] The signs, symptoms, and severity of TED can be worsened by both genetic and environmental factors. Smoking or exposure to cigarette smoke Smokers are twice as likely to develop Graves' disease Smokers with Graves' disease are over 7x more likely to develop TED, when compared to nonsmokers Smokers tend to have a longer duration of the active phase of TED (2-3 years for smokers, compared to 1 year for nonsmokers) Selenium deficiency [5] (see Selenium) Vitamin D deficiency [6] Increased stress levels (see Stress reduction) Mechanism of TED TED is caused by an inflammatory response involving the tissues in and around the eye socket. TED patients produce autoantibodies (proteins of the immune system that aberrantly react against the body's own cells) that bind to fibroblast cells within the eye socket When these antibodies bind, they cause the fibroblast cells to produce and release chemical signals and biologic materials that lead to swelling and congestion in and around the eye socket The main autoantibody produced by TED patients is known as Thyroid Stimulating Immunoglobulin (TSI), and this autoantibody can be measured in the blood to help monitor disease activity The amount of TSI present in a TED patient correlates with TED severity However, sometimes TED can occur without TSI formation Clinical Presentation of TED About 90% of patients with TED also have some thyroid dysfunction - usually the thyroid is overactive (i.e. Graves' disease), but occasionally the thyroid is underactive (e.g. Hashimoto's thyroiditis). Most times, the diagnosis of TED and diagnosis of a thyroid dysfunction occur within the same year. Patients who are diagnosed with TED but have no known thyroid dysfunction should see their primary care physician for an evaluation of their thyroid function. The disease course for TED involves 2 phases - active and stable. In the active phase there is active swelling and inflammation. This presents as redness in and around the eye, eye pain with or without eye movement, as well as swelling around the eyes and eyelids. The active phase of TED involves a waxing/waning period of these symptoms, and can last months to years. On average, the active phase of TED lasts about 1 year for non-smokers, and 2-3 years for smokers (or patients exposed to smoke). The active phase of TED spontaneously transitions to the stable phase, but can recur. Active TED has a recurrence rate of about 5-10%, but is less likely to recur after 18 months in the stable phase. Figure 3. Active vs. Stable TED. Active TED is characterized by signs of inflammation (swelling around the eye, swelling and injection of the conjunctiva, and enlargement of the muscles that move the eye). TED activity waxes and wanes, and usually transitions to stable TED within 1-3 years. Figure 4. Rundle's curve. As seen in the representation of TED activity over time in Rundle's curve, initiating therapy early is crucial to diminish the overall severity of the chronic disease. Many patients with TED present to a physician with similar complaints. The most common signs and symptoms associated with TED are Upper and/or lower eyelid retraction - the eyelid is pulled away from its normal resting position Affects up to 90% of TED patients, and can affect one or both eyes On exam, there is a larger palpebral fissure (the space between the upper and lower eyelids) and the eyes have a characteristic "startled/surprised" appearance In cases of severe retraction, it may become difficult to close the eyelids at rest, leading to dry eyes, which can lead to tearing, foreign body sensation, and blurred vision It is important to treat dry eyes, starting with liberal use of preservative-free eye drops, in addition to eye ointment at night Figure 5. Eyelid retraction is the most common presenting sign of TED, and is the result of many factors associated with TED. Figure 6. Lagophthalmos is the inability of the eyelid to fully close. It typically presents as dry eye, tearing, foreign body sensation, and blurred vision. Figure 7. Temporal flare. Note the elevation of the outer portion of the normal eyelid. Exophthalmos/Proptosis - bulging of the eyeball out of the eye socket Affects up to 60% of TED patients Most commonly leads to dry eye and excessive tearing It is important to treat dry eyes, starting with liberal use of preservative-free eye drops, in addition to eye ointment at night In severe cases, damage to the cornea can result This can be treated with the dry eye therapy listed above in addition to decreasing the palpebral fissure (distance between the upper and lower eyelids) with surgery to close the outer and/or inner corners of the eyelids (tarsorrhaphy), lowering the upper lid, raising the lower lid, or orbital decompression surgery (See Below) In rare cases, proptosis can cause globe subluxation, which is a displacement of the eye out of the eye socket This is an eye emergency, and needs to be addressed immediately Figure 8. Exophthalmos, also known as "proptosis," is when the eyeball is displaced out of the eye socket. This is an eye emergency – the cornea is at risk of drying out, and the optic nerve is at risk of irreversible damage. Restrictive extraocular myopathy - swelling of the muscles that control eye movement resulting in inadequate mobility of the eyes Affects up to 40% of TED patients One or both eyes are restricted in how far they are able to move In more severe instances, the eye muscles can be affected at rest leading to misalignment of the eyes This can cause strabismus (i.e. "crossed eyes"), which is a cause of diplopia (double vision). Permanent correction of restrictive myopathy is not typically performed until the patient has been in the stable phase of TED for several months. Temporary correction can be undertaken with adding prism lenses to the patient's glasses When the patient has been in the stable phase of TED for several (typically at least 6) months, surgical correction of strabismus can be considered Pain with eye movement Affects about 30% of TED patients Characterized as a dull, deep orbital pain Can usually be managed with over-the-counter NSAIDs Optic nerve dysfunction / compressive optic neuropathy Affects about 6% of TED patients The eye is encased in a confined, bony eye socket. With progressive inflammation and swelling of the muscles and tissues surrounding the eye, the pressure within the eye socket can increase, leading to damage of the optic nerve Warning signs include Decrease or change in color vision Decreased peripheral vision Decreased crispness of central vision This is an eye emergency, and needs to be addressed urgently by an ophthalmologist Figure 9. Hypotropia is when an eye is deviated downwards in comparison to the other eye, when looking straight ahead. This misalignment is due to an enlarged and restricted orbital muscle. Figure 10. Esotropia is when an eye is deviated inward in comparison to the other eye, when looking straight ahead. This misalignment is due to an enlarged and restricted orbital muscle. Figure 11. Chemosis is swelling within the conjunctiva. Figure 12. Conjunctival injection is caused by the dilation of the vessels within the conjunctiva. (larger image not available) Evaluating the Activity and Severity of TED When examining patients with TED, it is important to document both the current activity and severity of disease. This helps both the patient and physician track the course of the disease as well as monitor for signs and symptoms of "flare-ups" or disease recurrence. In addition, management is based on both the activity and severity of disease, making proper disease categorization of great importance in determining proper treatment strategies. To assess the activity level of TED, the Clinical Activity Score (CAS) can be used At the initial visit, patients are given a CAS score of 1-7 (one point for each of the following signs or symptoms) Spontaneous pain in or around the eye in the past 4 weeks (pain without eye movement) Eye pain associated with eye movement in the past 4 weeks Swelling of the eyelids Redness of eyelids Conjunctival injection (redness of the actual eyeball) Chemosis (swelling of the eyeball) Swelling of the caruncle (the red prominence at the inner corner of the eye) Figure 13 - Clinical Activity Score spontaneous orbital pain in last 4 weeks Gaze-evoked orbital pain in last 4 weeks Eyelid swelling Eyelid erythema Conjunctival injection Chemosis Inflammation of caruncle or plica semilunaris CAS ≥ 3 → "Active" - Criteria 1-7 Increase ≥ 2mm proptosis Decrease in uniocular motility in any one direction of ≥ 8° Decrease in visual acuity equivalent to 1 Snellen line CAS ≥ 4 → "Active" At subsequent follow-up visits, the 3 following criteria are added for a potential CAS score of 10 Increase in proptosis/exophthalmos (bulging of the eye out of the eye socket) of the eye (by at least 2mm) Decrease in motility of an eye in one direction (by at least 8º) Decrease in vision (by at least 1 line on the Snellen chart) TED is considered "active" if the CAS ≥ 3 at the initial visit, or ≥ 4 at follow-up visits To grade the severity of TED, many indices are used, two of which are mentioned below NOSPECS Class 0: No signs or symptoms Class 1: Only signs (upper lid retraction) Class 2: Soft tissue involvement (swelling of the eye or tissues surrounding the eye) Class 3: Proptosis (bulging of the eye out of the eye socket) Class 4: Extraocular muscle involvement (usually with strabismus) Class 5: Corneal involvement (severe dry eye from inability to adequately close the eye) Class 6: Sight loss (due to optic nerve involvement) The European Group of Graves' Orbitopathy (EUGOGO) classifies TED severity into three categories Mild Only a mild impact on daily life Insufficient signs/symptoms to justify immunosuppressive drugs or surgical treatment One or more of the following Minor lid retraction (