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The eye and thyroid disease

Ajay E Kuriyan, BA¹, Richard P Phipps, PhD^{2,3}, and Steven E Feldon, MD, MBA²

¹University of Rochester School of Medicine and Dentistry, University of Rochester Medical Center, Rochester, NY 14642, USA

²University of Rochester Eye Institute, University of Rochester Medical Center, Rochester, NY 14642, USA

³Department of Environmental Medicine, University of Rochester School of Medicine and Dentistry, University of Rochester Medical Center, Rochester, NY 14642, USA

Abstract

Purpose of review—The pathophysiology and optimal management of Thyroid Eye Disease (TED) have not yet been elucidated. Recent studies have increased our knowledge of the disease process and different diagnostic and therapeutic options. This review highlights the recent progress in TED research and identifies areas requiring further advancements.

Recent findings—The pathophysiology of TED likely involves genetic and environmental factors, which may potentiate cellular and humoral-mediated inflammation within the orbit. Despite progress in TED research, a target antigen has not been established with certainty.

New diagnostic methods and questionnaires are being developed that potentially provide information regarding inflammatory activity of TED. Corticosteroids alone or in combination with orbital radiation may be effective in improving TED symptoms. New immunomodulating therapies may also have a role TED management. Surgery is highly effective for treatment of TED-induced optic nerve compression and for managing the chronic soft tissue changes of TED.

Summary—A unifying hypothesis of TED pathophysiology is elusive. Further bench research into the autoimmune process is needed. In addition, large, prospective, randomized clinical trials, based on the inflammatory activity of disease, while difficult to design, are essential to develop a consensus regarding the proper timing and use of anti-inflammatory medications.

Keywords

Thyroid Eye Disease; Graves' Ophthalmopathy; Graves' Orbitopathy; Thyroid associated ophthalmopathy; Graves' Disease

Introduction

Thyroid Eye Disease (TED), also called thyroid associated ophthalmopathy (TAO) and Graves' ophthalmopathy/orbitopathy (GO), is the most common orbital disease, affecting 25%-50% of patients with Graves' Disease (GD) [1]. Clinical symptoms and signs are usually mild, consisting of ocular irritation with redness and tearing, "stare" due to lid retraction and exophthalmos, and periorbital swelling. Approximately 28% of TED cases are severe, with

Contact details for corresponding author: Steven E. Feldon, MD, MBA, Phone: (585) 275-1126, Fax: (585) 273-1043, steven_feldon@urmc.rochester.edu, Address: University of Rochester Eye Institute, 210 Crittenden Blvd., Box 659, Rochester, New York 14642.

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restricted motility leading to diplopia, exposure keratopathy, and optic neuropathy [2,3•]. Patients with severe TED may have lower rates of remission of their thyroid disease compared to mild TED patients [4•]. Despite ongoing basic science and clinical research, highly effective therapeutic strategies remain elusive.

Pathophysiology

In TED, the dramatically enlarged extraocular muscles and increased orbital fat results from a complex interplay among orbital fibroblasts (OF), immune cells, cytokines, autoantibodies, genetics, and environmental factors [1]. However, clear and indisputable identification of a target antigen has not been established.

Autoimmunity

Lehman and colleagues summarized a plausible pathway for fibroblast activation in TED (Figure 1) [5•]. In this scenario, autoantibodies specific for fibroblast surface thyroid-stimulating hormone receptor (TSH-R) and insulin-like growth factor-1 receptor (IGF-1R) are proposed initiators of orbital inflammation [1,5•]. However, increased TSH-R and IGF-1R expression occur with adipogenesis, providing an alternative, non-causative explanation for their presence in TED orbits [1,6].

Autoantibody stimulation activates fibroblasts to release chemokines and cytokines, promoting lymphocyte migration and B cell maturation [5•]. Interaction with humoral and cell-mediated elements of the immune system via OF surface CD40 and human leukocyte antigen-DR (HLA-DR), may lead to increased autoantigen presentation and further release of cytokines. Prostaglandin E₂ (PGE₂), IL-6, and IL-8 may act on OFs to promote proliferation and production of glycosaminoglycans (GAG), increasing extraorbital muscle mass. Prostaglandin D₂ (PGD₂) and 15-deoxy-Δ^{12,14}-Prostaglandin J₂ (15d-PGJ₂), may act on an OF transcription factor called peroxisome proliferator-activated receptor-γ (PPARγ), leading to OF adipogenesis and increased orbital fat. Cyclooxygenase – 2 (COX-2) expressed by OFs increases synthesis of the involved prostaglandins. Vondrichova and colleagues demonstrated that COX-2 and stearoyl-coenzyme A desaturase (SCD), an adipose tissue marker, are overexpressed in orbital tissue from TED patients with active, compared to chronic, disease [7•].

In co-cultures, autologous T-lymphocytes stimulate TED OF proliferation [8]. Chen and colleagues demonstrated that there is more infiltration of macrophages and higher mRNA levels of a macrophage chemoattractant called C-C motif chemokine ligand-2 (CCL2)/monocyte chemoattractant protein-1 (MCP-1) in the orbital fat compared to normal controls [9••].

Smoking

Cigarette smoking is a risk factor for the development and severity of TED [1]. Cawood and colleagues established that OF exposed to cigarette smoke extract (CSE) have a dose-dependent statistically significant increase in GAG production and adipogenesis [10••]. Moreover, IL-1 and CSE had a synergistic effect on adipogenesis.

Genetics

Bednarczuk and colleagues cited conflicting evidence from case-control studies examining the association between TED and genes involved in inflammation, such as HLA, cytotoxic T-lymphocyte antigen-4 (CTLA-4), tumor necrosis factor (TNF), interferon-γ (IFN-γ), intercellular adhesion molecule-1 (ICAM-1), and TSH-R [11•]. Based upon these

investigations, either a unifying polymorphism has yet to be identified or TED has a multifactorial inheritance pattern.

Syed and colleagues found an association between mild/moderate TED and certain single nucleotide polymorphisms (SNPs) in the protein tyrosine phosphatase (PTP) called PTPN12, which interacts with the TSH-R, the proposed target of autoantibodies in GD [12••]. Furthermore, SNPs in the pro-inflammatory IL-23 receptor, which affects T lymphocyte phenotype, were shown to be significantly associated with TED by Huber and colleagues [13••].

NF- κ B1, a transcription regulator, is activated by several stimuli, including cytokines. Polymorphisms of NF- κ B1 are associated with several chronic inflammatory and autoimmune diseases [14••]. Kurylowicz and colleagues established a correlation between a polymorphism in the NF κ B1 gene promoter ((-94ins/del ATG) and the development and age of onset of TED within a Japanese cohort [14••].

Chong and colleagues found a positive trend between an IL-13 SNP (2044G/A) and the development of proptosis in a study population of Chinese children [15•]. Boyle and colleagues demonstrated that certain polymorphisms that confer hypersensitivity of the glucocorticoid receptor, which has an anti-inflammatory effect, were associated with less severe TED [16••]. Akaishi and colleagues studied the frequency of the class II major histocompatibility complex (MHC) HLA alleles in 81 Brazilian TED patients and 161 normal controls. TED patients with major extraocular muscle involvement were found to have a higher frequency of the HLA-DRB1*16 allele, while patients with minor extraocular muscle involvement were found to have a higher frequency of the HLA-DRB1*03 allele [17••].

Clinical Research

Diagnostic techniques, standardized scoring systems, psychological impact assessment, as well as pharmacological and surgical therapies are areas of clinical TED research.

Diagnostic testing modalities

Majos and colleagues studied magnetic resonance imaging (MRI) of 40 orbits to examine the correlation between extraocular muscle volume and the measurement of signal intensity (SI) and T2-time (T2-t), which they considered indicators of inflammation [18••]. Both SI and T2-t were found to have statistically significant correlations with volumes of most of the extraocular muscles. This study did not directly correlate the findings of T2-t and SI with clinical symptoms.

Using digital infrared thermal imaging to diagnose early TED, Chang and colleagues studied 32 control orbits and 28 TED orbits. They found a significantly increased temperature among the TED orbits [19••]. A positive correlation was noted between the severity of TED and temperature. Also, a significant decrease in the temperature was found after pulse methylprednisone therapy.

Another tool to measure orbital inflammation is the use of radioactively labeled substances, such as ⁶⁷gadolinium (Ga) citrate and ^{99m}technetium (Tc)-labeled agents [20••]. Reyhan and colleagues prospectively studied the use of ^{99m}Tc(V)-dimercaptosuccinic acid (^{99m}Tc(V)-DMSA) in 28 TED patients and found a significant correlation between uptake of the agent and Clinical Activity Score (CAS) [20]. Another study by Sun and colleagues demonstrated a correlation between ^{99m}Tc-HYNIC-Octreotide uptake and CAS in 14 TED patients [21••]. This study also showed a significant difference in orbital/occipital uptake ratio between TED patients who were responders to retrobulbar irradiation and those who were not.

Clinical classification systems

Severity scores assess TED in a standardized fashion and are especially important in clinical trials. Two such scoring systems are the modified NOSPECS and the CAS systems [22,23]. The modified NOSPECS criteria includes lid retraction, soft tissue inflammation, proptosis, size difference, extraocular muscle involvement, corneal defects, and optic nerve compression [23]. The CAS includes pain, redness, swelling, and impaired visual function, which may signal acute inflammation [22]. Both measure symptom severity.

Dolman and Rootman included subjective and objective components combining aspects of NOSPECS and CAS, with subjective input from the patient about how they feel about their TED status [24]. The so-called VISA classification includes Vision (presence or absence of optic neuropathy), Inflammation (0-8 or mild, moderate, or severe), Strabismus (0-3), restriction (0-3), and Appearance/exposure (mild, moderate, or severe). In future studies, scoring systems should be compared directly to purported objective measures of inflammation, such as the MRI SI and T2-t, thermography, and the radioactive uptake studies described previously.

Psychological and Quality of Life Impact

Disfigurement and visual changes of TED have a large impact on patients' psychological state and quality of life (QOL). Bradley and colleagues examined the use of the National Eye Institute Visual Function Questionnaire (NEI VFQ-25) to assess the effect of TED on QOL in a 30 patient cross-sectional study [25]. Moderate impairments were in the Mental Health and Role Difficulties categories. However, two-thirds of patients felt the questionnaire was not appropriate to assess the impact of TED. Estcourt and colleagues noted development of altered identity in taped, semi-structured interviews of 25 TED patients [26•].

Treatment Trials

Variation in presentation of TED symptoms and signs, as well as difficulty in assessing autoimmune activity complicates study design. Obstacles include small sample sizes, as well as heterogeneity of response to anti-inflammatory and immunomodulatory therapy.

Corticosteroids—In a review by Rajendram and colleagues, glucocorticosteroid response rate ranges from 63-77% [27]. Due to their side-effects, use is often limited to three to five months. Disease recurrence after cessation of glucocorticosteroids is common.

A review by Zoumalan and colleagues found that weekly pulse doses of intravenous glucocorticosteroids produced a more favorable response in more patients than oral glucocorticosteroids given daily (74.6 vs. 55.5%) [28••]. Case reports of severe morbidity or mortality following intravenous glucocorticosteroids treatment for TED have been published, tempering enthusiasm for this route [29,30]. Le Moli and colleagues reported dose-dependent liver damage due to the effect of glucocorticosteroids on hepatocytes [31••].

Radiation—Bradley and colleagues performed a systematic review of nine randomized controlled trials and five observational studies with >100 patients on the use of orbital radiation as a treatment for TED [32••]. Based on the randomized controlled trials, orbital radiation did not yield improvement in proptosis, eyelid retraction, nor soft tissue changes. Radiation retinopathy occurred in one to two percent of patients. There was conflicting evidence from the randomized controlled trials regarding the improvement of ocular motility and the one study that examined its effect on QOL had inconclusive findings. However, a meta-analysis by Wei and colleagues, which included data from eight cohort studies and 10 randomized controlled trials, examined the effect of orbital radiation and found that radiation was more effective than a vehicle control and as effective as steroids alone [33•]. The use of combined corticosteroids

and orbital radiation varied in the studies reviewed by Bradely and colleagues [32••]. Wei and colleagues found radiation and steroid combination therapy to be more effective than either used alone [33•]. Zoumalan and colleagues' observations were similar [28••].

New Immunomodulation Therapies—Etanercept, which has an extracellular binding site for TNF α , an inflammatory cytokine, decreases the level of biologically active TNF α [34•]. Possible side-effects include infections, malignancies, and the development of additional autoimmune disorders [34•].

Paridaens and colleagues performed a pilot study using biweekly 25mg etanercept subcutaneous injections for 12 weeks in 10 euthyroid, recent onset TED patients with a mean pretreatment CAS of 4 (range: 3-6) [34•]. Mean CAS decreased to 2.6 at six weeks and 1.6 at 12 weeks [34•]. No toxicity was noted.

Rituximab is a monoclonal antibody directed against CD20, a B lymphocyte surface antigen [35••]. Possible adverse reactions with rituximab include infusion reaction, serum sickness, and increased infections. Targeting B cells should theoretically eventually dampen the inflammatory process in TED [35••].

Salvi and colleagues reported a steroid refractory case of TED with improvement of CAS after rituximab treatment and no histological evidence of lymphocyte infiltrate in orbital tissue removed during decompression surgery [36]. However, a pilot study of GD patients comparing rituximab and methimazole with methimazole monotherapy by El Fassi and colleagues found no difference in TSH-R antibody levels between the groups [35••].

Rapamycin is an antibiotic in the macrolide class, which also has anti-inflammatory and anti-fibroblast actions via inhibition of cytokines and growth factor-mediated proliferation of fibroblasts and immune cells [37•]. Possible adverse reactions associated with rapamycin include myelosuppression (most often thrombocytopenia) and hyperlipidemia.

Chang and colleagues reported a case of TED with dysthyroid optic neuropathy that was refractory to steroids and decompression surgery, but improved gradually when treated with rapamycin in conjunction with prednisone taper [37•]. The patient developed hyperlipidemia during rapamycin treatment.

Surgical Therapy—TED surgeries may relieve acute optic nerve compression in dysthyroid optic neuropathy and effectively mitigate the sequelae of chronic orbital inflammation.

Orbital Decompression—Exophthalmos and apical compression of the optic nerve are indications for orbital decompression involving bone. In a study by Jernfors and colleagues, 76% of patients felt that the surgery was very helpful [38•]. There was minimal improvement in diplopia and late complications included sinusitis (18%), oroantral fistula (3%), sensory disturbances (32%), facial neuralgia (13%), operation-induced diplopia (8%), and vision loss (3%). When comparing the complications (except operation-induced diplopia) to normal, matched controls, only sensory disturbances occurred significantly more frequently.

Fat removal orbital decompression removes orbital contents rather than accommodating them within a larger socket. Richter and colleagues performed a retrospective study of transpalpebral fat removal orbital decompression on 1,374 patients and found a decreased mean proptosis of 5.9 mm, improved symmetry of eye protrusion, improved visual acuity, and improvement in QOL (data unpublished). There were no cases of diplopia postoperatively [39•]. Wu and colleagues performed fat removal orbital decompression on 222 orbits in Taiwan and found a mean postoperative reduction of proptosis by Hertel measurement of 3.6 mm (range: 1.5 to

7.5, SD: 1.0) and improved diplopia in 20% (3/15) of patients with preoperative diplopia [40••]. Only 2.8% (3/105) of patients developed diplopia postoperatively.

Extraocular Muscle Surgery—Thomas and colleagues, based on previous studies, reported the success rate of extraocular muscle surgery in TED varies from 43% to 82% [41•]. Controversy exists as to whether surgical decision-making should be based upon reducing restriction of involved muscles or the degree of deviation between the eyes. In a study of 137 TED patients by Nguyen and colleagues, a higher success rate and lower re-operation rate was found when correcting for the restricted duction compared to deviation [42]. Dal Canto and colleagues confirmed the success of this method in a more recent study of 24 TED patients [43]. On the other hand, Thomas and colleagues found no significant difference in the rate of successful outcomes in a retrospective study of 86 patients comparing the two approaches ($p=0.55$) [41•]. Yan and colleagues retrospectively studied 27 TED patients with large angle strabismus ($>25^\circ$) and found that 74% (20/27) of cases were successfully treated with single extraocular muscle recession, suggesting that for the majority of large angle strabismus, single extraocular muscle surgery is adequate [44•].

Medical and Surgical Recommendations

On behalf of a European consortium studying TED, Bartalena and colleagues published the set of medical and surgical recommendations shown in Figure 2 [45••,46]. They felt that joint management by endocrinology and ophthalmology was optimal.

While many of their suggestions such as cessation of smoking and ocular surface management are common practice, their advocacy of IV steroids, as well as orbital radiation, is controversial and requires further study.

Our approach to management of TED is to use conservative measures for mild to moderate disease directed toward patient comfort. Artificial tears, nocturnal lid taping, elevating the head of the bed and occasional use of diuretics are often sufficient in the active stage. Chronic soft tissue alterations are treated surgically. Severe TED, particularly when accompanied by optic neuropathy, is managed using high dose oral prednisone. If full taper cannot be achieved within 2 months, then bony orbital decompression is performed. Orbital radiation is considered an adjunct to steroids, decompression, or both for recalcitrant disease. Immunosuppressive and immunomodulatory drugs are not generally utilized.

Future Directions

Understanding the autoimmunity of TED is crucial to improve patient management, especially during active disease. Unfortunately, there are no accepted biomarkers associated with “active” TED, nor are there biomarkers predictive of developing severe disease. Drugs that could suppress early, active TED all have substantial side-effects. Therefore, in the absence of predictive diagnostic or clinical signs, the risk:benefit ratio of treatment may be adverse. Furthermore, many of the inflammatory symptoms and signs may reflect consequences rather than causes of disease. For instance, ocular surface exposure and compartment syndrome may produce substantial non-specific inflammation partially responsive to anti-inflammatory therapy. Anti-fibrotic agents may prove more effective than immune suppressant therapy late in the disease process.

Questionnaires designed to assess autoimmune inflammatory activity must be validated against objective measures of inflammation. In the future blood tests looking at inflammatory markers of TED may prove highly beneficial in planning therapy. Soluble CD40, CD154, vascular cell adhesion molecule-1, and matrix metalloproteinase-9 or urine tests for oxidative stress, such as urinary 8-OHdG levels, are possible examples [47•,48•,49•].

Conclusion

Great strides have been made over the past year in many aspects of TED research, especially regarding the pathophysiology of TED, assessment of inflammatory activity, and novel uses of immunomodulating therapies. New medical and surgical management options have been introduced, while traditional therapies have been further studied. Much research remains to be done in the field of TED pathophysiology in order to provide insight regarding risk factors, targets for therapy, and the ideal window for anti-inflammatory versus anti-fibrotic treatments. Large, prospective, randomized, controlled clinical trials must be designed around proper assessment of subjects' inflammatory status. These studies will lead to a consensus regarding management of TED.

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Figure 1. Pathophysiology of TED

According to one current model, TED is triggered by binding and activation of orbital fibroblasts by autoantibodies. These autoantibodies could be specific for antigens such as TSH-R and/or IGF-1R. Activated orbital fibroblasts release chemokines, including IL-16, RANTES, and CXCL10, which recruit T lymphocytes into the orbit. These lymphocytes then interact with fibroblasts, potentially activating each other, further promoting cytokine production (IFN γ , TNF α , PGD $_2$, and 15d-PGJ $_2$) and secretion of T cell-activating factors by the fibroblasts (IL-8 and CXCL10). Fibroblasts are also stimulated to secrete IL-6 (promoting B cell differentiation) and to increase autoantigen presentation, both of which amplify the overall response. The interactions of fibroblasts with T cells result in the deposition of extracellular matrix molecules, fibroblast proliferation, and fat accumulation.

See Lehmann, GM [5].

Figure 2. Management of Graves' orbitopathy

Rehabilitative surgery includes orbital decompression, squint surgery, lid lengthening, and blepharoplasty/browplasty. i.v. GCs, intravenous glucocorticoids; OR, orbital radiotherapy; DON, dysthyroid optic neuropathy.

See Bartalena L. [45]