

IMMUNOLOGY OF THYROID EYE DISEASE: NEW TREATMENTS ON THE HORIZON?

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LEARNING OBJECTIVES

1. List two autoantigens of Graves' disease and TAO.
2. Describe pathogenesis of TAO in terms of unique properties of orbital fibroblasts.
3. Describe the role of cytokine in TAO pathogenesis.

CME QUESTIONS

1. List 2 autoantigens implicated in TAO.
2. True or False: Rituximab has shown promise in the treatment of TAO.
3. True or False: Early anti-inflammatory treatment has been clearly demonstrated to slow disease progression including development of strabismus and proptosis.

KEY WORDS

1. Thyrotropin Receptor
2. TAO
3. Graves' Disease
4. IGF-1R (Insulin Like Growth Factor-1 Receptor)
5. Fibrocytes

I. INTRODUCTION

GD is an autoimmune disease where circulating antibodies cause hyperthyroidism and lead to thyrotoxicosis. These antibodies, originally referred to as long-acting thyroid stimulators, are directed against the thyrotropin receptor (TSHR). They mimic the agonist activity of TSH but are not subject to the normal feedback in the anterior pituitary. GD is approximately 7 to 10 fold more frequent in women, and typically occurs between 20 and 50 years of age. Clinical manifestations of GD encompass thyroid enlargement and thyrotoxicosis, inflammation and remodeling of the orbit, and rarely the skin. The orbital disease is collectively known as thyroid-associated ophthalmopathy aka thyroid eye disease (TED). It is unclear why anatomically unrelated tissues undergo coordinate and selective immune infiltration and remodeling. Furthermore, the mechanistic basis for the self-limited course of the orbital disease is unclear, but identifying these underlying factors could provide insights necessary for the development of effective therapies. This article summarizes our current understanding of TED,

focusing on the fundamental aspects of its molecular pathogenesis. In it we identify attractive potential targets for interrupting the disease.

II. IMMUNOLOGY OF GD

Adults normally exhibit tolerance to antigens that are present during fetal life and thus are recognized as "self." However, under certain circumstances, tolerance may be lost leading to immune reactions against self, manifesting clinically as autoimmune disease. Proposed mechanisms for autoimmunity include molecular mimicry, abnormal protein modification, release of ordinarily sequestered antigens, and epitope spreading.

While GD is a systemic disease, its manifestations exhibit an anatomic-site selective predilection. Thyroid dysfunction is the principal hallmark of GD and occurs in greater than 90% of patients sometime during the course of their disease. Hyperthyroidism results from activating antibodies which bind to TSHR on thyroid epithelial cells and mimic the actions of TSH. Overall, the clinical manifestations of glandular GD are predictable and can be treated with relative ease in the vast majority of patients.

III. CLINICAL COURSE OF TED

Approximately 25–50% of patients with GD develop TED, while sight threatening disease occurs in 5% of patients. Conversely, 10% of those manifesting TED fail to become hyperthyroid. Regardless of whether thyroid dysfunction or TED develops first, the other becomes apparent within 18 months in 85% of patients with GD. Rundle was the first to divide the course of TED into active (dynamic) and inactive (static) disease phases. Signs and symptoms of active TED include proptosis, conjunctival injection, chemosis, diplopia, corneal ulceration, and rarely loss of sight from optic nerve compression. The tissue expansion occurs within the relatively fixed volume imposed by the bony orbit and results from inflammation, accumulation of glycosaminoglycans (GAGs), and increased fat content.

Inactive disease is characterized by stable proptosis, eyelid retraction, and may be accompanied by persistent restrictive strabismus and the resolution of inflammation, usually within 18–24 months of its first appearance. The self-limited nature of TED is peculiar among human autoimmune diseases. Anti-inflammatory therapy, such as glucocorticoid steroids are effective only during the active phase, whereas surgical intervention is usually performed once this phase has subsided.

IV. IMMUNOLOGY OF TED

The active phase of TED is characterized by orbital and periorbital inflammation targeting connective tissue and fat. Electron and light microscopy suggest that the muscle cells remain intact early in the disease. However, intense infiltration of T lymphocytes, mast cells and occasional B cells often intercalate between extra-ocular muscle fibers and can be found in orbital fat, suggesting that connective tissue and represents the primary autoimmune target.

Immunohistochemical evidence of cytokines, including interferon- γ (IFN- γ), tumor necrosis factor- α (TNF- α), and interleukin-1 α (IL-1 α) has been reported in the connective tissues and their presence is associated with T cell infiltration. These cytokines may be produced by infiltrating mononuclear cells and resident fibroblasts since they are also detected in areas devoid of mononuclear infiltration. Specifically, IL-1 α is a proinflammatory cytokine produced by monocytes, macrophages, and fibroblasts that may play a critical role in promoting inflammation and extracellular matrix proteins. Extensive deposition of hyaluronan in the interstitium dominates the histological picture of TED, and is associated with orbital tissue expansion.

Factors underlying the spontaneous resolution of inflammation in TED remain unidentified. The possibilities include declining auto-antigen abundance or reduced antigen presentation. The targets of other autoimmune diseases, such as synovial tissue in rheumatoid arthritis, exhibit recognizable lymphoid structures. In contrast, the orbit lacks these structures. Thus, TED is not associated with the lymphoid neogenesis that might be crucial to sustained immune activation.

Role of orbital fibroblasts in the pathogenesis of TED

Several studies have demonstrated that orbital fibroblasts, especially those from patients with GD, are unique with respect to how they respond to several proinflammatory cytokines. The divergent phenotype of these cells may underlie the anatomic site-selective manifestations of GD. Orbital fibroblasts (OF), unlike dermal fibroblasts, fail to generate adequate levels of soluble IL-1 receptor antagonist. This would allow poorly opposed IL-1 β signaling. They also exhibit enhanced production of extracellular matrix components such as hyaluronan in response to these cytokines (Figure 2). Thus, GD OF produce proinflammatory molecules and components of connective tissue that lend themselves to the site-specific tissue remodeling occurring in TED.

T cells may also play an important role in OF activation through increased expression of CD40 on the latter. CD40 binds CD40 ligand (aka CD154) displayed on the surface of T lymphocytes and provides T cell co-stimulation that results in clonal expansion of naïve T lymphocytes and enhances pro-inflammatory cytokine production, including that of IL-1, IL-6 and IL-8. Actions of these in turn activate the expression of PGHS-2, hyaluronan synthase (HAS), and UDP glucose dehydrogenase (UGDH) genes, leading to inflammation and hyaluronan production. Thus, disruption of fibroblast - T cell

interactions mediated by CD40-CD40ligand could represent an important therapeutic target in TED. Administration of therapeutic blocking antibodies against to CD40 ligand already has proven effective in pre-clinical mouse models of diabetes and inflammatory bowel disease.

B lymphocytes in GD and their implications in therapy design

In addition to their function as precursors for antibody-secreting plasma cells, B cells efficiently present antigen and produce important cytokines. B cell-deficient mice cannot generate T cell responses following immunization with TSHR and thus these cells are probably essential to the initiation of autoimmune thyroid disease. Autoantibody generation is also dependent on the complex interplay between B and T cells. Thus, B cell-depleting therapies and those which interrupt interactions between cognate molecules on B cell surfaces offer great promise in the context of autoimmune disease. An important example of these therapies, rituximab (RTX), represents a monoclonal antibody that binds the B cell surface antigen CD20. RTX blocks cell proliferation and attenuates CD20-dependent B cell maturation. Plasma cells do not express CD20 and are thus spared from the cell-depleting actions of RTX. Despite this lack of plasma cell depletion, the agent reduces antibody-mediated responses by blocking antigen presentation and cytokine production. RTX was developed for the treatment of B cell non-Hodgkin's lymphomas. Experience with B cell depletion in TED has been limited to uncontrolled studies but remains encouraging. Two case reports showed significant reduction in the clinical activity in patients with TED unresponsive to steroids. A prospective, controlled study demonstrated sustained remission of hyperthyroidism in GD patients treated with RTX even though the drug failed to influence autoantibody levels.[104] In another open, non-randomized study of patients with TED, RTX was compared to intravenous glucocorticoid therapy. Patients receiving RTX demonstrated greater improvement of the clinical activity score with fewer side effects (33 vs. 45% of patients) than those treated with glucocorticoids. Thyroid function and TRAb levels were unaltered following RTX treatment.¹⁰⁴ Adverse effects related to RTX include transient hypotension, cough, itching, mild temperature elevation, and potentially, infection. However, most studies have failed to demonstrate significantly increased infection rates. Thus, RTX appears to represent a promising therapeutic agent in a subset of patients with TED. Well-controlled, prospective, and adequately powered studies remain essential to fully evaluate its role in these patients.

Autoantigens in TED

The search for relevant antigenic triggers in GD and TED has broadened considerably in the wake of findings that other autoimmune processes involve multiple autoantigens. Both genetic and environmental factors have been implicated. The role of TSHR is firmly established in the pathogenesis of hyperthyroidism in GD. But the other facets of this disease, including those occurring in the

connective tissue are not easily reconciled with the TSHR representing the single pathogenic antigen. IGF-1R has been implicated in the pathogenesis of TED by virtue of several pieces of evidence recently generated by our research group. Multiple non-pathogenic autoantibodies are frequently detected in autoimmune disease, generated as a consequence of tissue damage. Thus, a role for any of these proteins and the antibodies directed against them in TED remains to be demonstrated

Role of TSHR

The role of TSHR and its antibodies in the pathogenesis of TED remains uncertain. Several interesting correlations between antibody levels and disease activity have been reported.⁸⁹ TSHR expression in human fat tissue was first suggested when TSH was found to mediate lipolysis in fetal and newborn adipocytes but not in adult adipocytes. TSHR mRNA has been detected in orbital tissues and OF, albeit at extremely low levels and undifferentiated fibroblasts fail to respond to rhTSH. Clearly additional studies will be required if we are to establish an important role for TSHR in the pathogenesis of TAO.

Role of IGF-1R

The IGF-1/IGF-1R pathway has been implicated in the pathogenesis of many malignant and autoimmune diseases. More than 20 yrs ago, IGF-1 immunoreactivity was demonstrated on the surface of extra-ocular muscle and orbital fat cells from 2 patients with TED. Subsequently, the fraction of IGF-1R⁺ fibroblasts cultured from the orbit, skin, and thyroid of patients with GD was found to be increased. Treatment of these fibroblasts with either IGF-1 or GD-IgG results in the synthesis of two powerful T cell chemoattractants, namely IL-16 and RANTES, as well as the generation of hyaluronan. Importantly, neither IGF-1 nor GD-IgG elicited these responses in fibroblasts from individuals without autoimmune disease. These findings suggest that the increased levels of IGF-1R may play a role in the pathogenesis of GD. Anti-IGF-1R antibodies were detected in most patients with GD but in few individuals without the disease.

Like fibroblasts, T and B cells from patients with GD exhibit a striking phenotypic skew toward the IGF-1R⁺ phenotype. Notably, CD45RO⁺ T cells, representing memory T cells, exhibit remarkable IGF-1R skew, especially those with the CD8⁺ phenotype. Display of IGF-1R imparts a growth advantage and protects from Fas mediated apoptosis among T cells and is associated with the production of anti-TSHR antibodies in B cells. These findings suggest that IGF-1R may participate in the development of GD. Evidence that TSHR and IGF-1R might be functionally linked was strengthened recently when these proteins were found to co-localize. These receptors may form both physical and functional complexes since TSHR signaling to ERK activation could be attenuated by an IGF-1R blocking antibody. Several strategies for disrupting IGF-1R signaling have been developed recently and are currently being evaluated as therapy for cancer.

Role of Cytokines and immune mediators

TNF- α levels may be elevated during the inflammatory phase of TED. Disruption of this pathway has become a major and highly successful approach to the therapy of rheumatoid arthritis and Crohn's disease. Three biological anti-TNF- α agents are currently in wide clinical use including the monoclonal antibodies, infliximab and adalimumab. Etanercept, a recombinant human soluble TNF- α receptor fusion protein, binds and inhibits TNF- α activity. Two separate reports of infliximab use in patients with TED suggest that it might reduce inflammation and improve visual function without side effects. In the first study, nearly complete resolution of inflammation was observed within 72 hours following drug administration and improvement in visual acuity and color vision occurred over the subsequent week.

VI. CONCLUSION

Despite intensive study, identity of the proximate antigenic target initiating TED and the relationship between the orbital disease and the other components of GD remain uncertain. Lack of a pre-clinical disease model continues to plague our efforts to better understand this disease. Important insights concerning the pathogenesis of allied autoimmune diseases and increasing knowledge about their successful treatment should shed new light on the fundamental factors underlying TED and facilitate development of therapies for this particularly vexing process.

CME ANSWERS

1. TSHR and IGFR
2. True
3. False

OBJECTIVE MARKERS FOR THYROID EYE DISEASE (TED) ACTIVITY, SEVERITY AND PROGRESSION

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LEARNING OBJECTIVES

1. To understand the clinical difference between active and chronic thyroid eye disease.
2. To outline the challenge of identifying which TED patients are at risk for developing significant visual disability and dysfunction.
3. To review the current serum and imaging measures that have been used to quantify TED disease activity and predict outcome.

CME QUESTIONS

1. What is the difference between active and chronic thyroid eye disease?
2. Name four objective markers that have been explored in TED?
3. Name an objective marker you could integrate into your clinical practice?

KEYWORDS

1. Graves' Disease
2. Thyroid Eye Disease
3. TED Activity
4. TED Severity
5. TED Progression

INTRODUCTION

Thyroid eye disease (TED) also called Graves' ophthalmopathy, can result in visual disability, including blurred or double vision, visual loss, discomfort, and facial disfigurement. These manifestations are associated with auto-immune-mediated inflammation in orbital and periorbital tissues and culminating in irreversible remodeling. Thus, we now propose the **hypothesis** that effective treatments of TED should target the disruption of inflammation early in the disease. However considerable controversy exists as to whether intervention might alter the ultimate outcome of the natural disease course. Confounding this vexing issue is an absence of a validated and uniformly accepted method of measuring treatment outcome.

HYPOTHESIS OF THE PROPOSED TED TREATMENT TRIAL (TEDTT)

Treating early, active TED of clinical importance will result in diminished severity and duration of active TED and result in less facial disfigurement, and visual disability and a better quality of life.

SUMMARY OF CRITICAL DEFICIENCIES IN PRIOR STUDIES ATTEMPTING TO ASSESS EFFICACY OF ANTI-INFLAMMATORY TREATMENTS

- Failure to objectively define clinical activity
- Failure to objectively assess whether duration and severity of active phase of disease was altered
- Exclusion of patients with severe active disease or optic neuropathy
- Inclusion of patients with chronic, inactive TED
- Failure to treat radiated patients with concomitant corticosteroids
- Use of early cross-over sham radiation
- Short follow-up that fails to address long-term disfigurement and disability
- Inadequate statistical power

NEW MEASURES ARE ESSENTIAL TO ASSESS TED SEVERITY, DURATION OF ACTIVITY AND TREATMENT OUTCOME IN TEDTT

The duration (months to years) and severity of active TED are unpredictable in individual cases. Male gender, older age, degree of initial thyroid imbalance, prolonged hypothyroidism and cigarette smoking are risk factors for longer duration and severity of the initial active phase. The most widely utilized disease activity classification system is NOSPECS which documents the presence of specific symptoms and signs of which only some are characteristic of active disease. A higher ("clinical worsening") may not represent increased inflammatory activity, but rather progressive fibrosis associated with resolving inflammation. More recently, the modified clinical activity TED score (CAS) has been used. The CAS assigns a point to each symptom or sign (retrobulbar pain, eyelid erythema, conjunctival injection, chemosis, swelling of the caruncle, eyelid edema or fullness) and is a simple summation that does not provide information regarding

overall progression or severity of TED. In practice, the identification of active TED remains an imperfect combination of the patient's impression and the clinician's interpretation of the physical signs.

OBJECTIVE DISEASE ASSESSMENT TOOLS

Potential candidates for objective assessment of TED disease activity currently include: (1) eye muscle reflectivity (EMR) on A-mode ultrasound of 40% or less (2) increased urine or plasma glycosaminoglycans (GAGs) (3) high orbital uptake on Octreoscan; (4) increased thyroid stimulating immunoglobulin detection of extraocular muscle edema by MRI. Because GAG assessment and Octreoscan are not widely available and ultrasound is too operator dependant, MRI and serum immunology appear to have the best potential objective outcome measures for the future TEDTT.

PRELIMINARY EVALUATION OF SERUM IMMUNOLOGY MEASURES

Laboratory tests to detect thyroid dysfunction, including thyroid stimulating hormone, thyrotropin, and serum free T3 and T4 levels, do not correlate with TED disease activity. Thyroid stimulating immunoglobulins (TSI), in contrast, have been found in more than 90% of patients with active GD and in 50–90% of euthyroid TED patients. Also, TSI levels are significantly higher in Graves (GD) patients **with** TED; higher TSI levels also correlate with the presence of active TED signs such as eyelid edema. TSI levels have been found to be higher in patients with EOM and orbital fat expansion on orbital CT, but correlation with MRI characteristics has not been performed.

TED is also associated with antibodies that recognize and activate the insulin growth factor (IGF-1) receptor. Virtually all individuals with early GD and TED exhibit antibodies that bind to the IGF-1 receptor and activate this protein. There is a specific relationship between these antibodies and receptor activation in orbital fibroblasts from patients with severe TED.

TSI is considered elevated if over 125; active TED patients often have levels in the 300–500 range. TSI levels drop as TED becomes inactive. In contrast, anti-IGF-1R is not detectable in patients without an active autoimmune disease such as TED, so the test result is either positive or negative. In TED and not a continuous variable. In summary, patients with GD and TED have higher levels of TSI compared to patients with GD alone. Elevation of TSI appears to be a prerequisite for the development of active TED. IGF-1 is elevated in early, active TED and GD. In contrast, other antibody levels (TBI, anti-thyroid peroxidase and anti-thyroglobulin) are often found to be significantly lower in GD/TED patients compared to GD alone.

PRELIMINARY EVALUATION OF MAGNETIC RESONANCE IMAGING OPTIONS

A small number of studies have explored the utility of MR imaging as a tool to identify extraocular (EOM) enlargement and quantitate EOM edema. The MR image acquisition is predicated on the differential behavior of soft tissues in a magnetic field, which is based primarily on the water content of the tissues. The increased water content caused by active inflammation is characterized by prolonged T2 relaxation times (a continuous variable) and by decreased gadolinium contrast enhancement of fat-saturation T-1 imaging (a subjective interpretation).

MR results were compared to subjective, non-validated clinical and often inadequate measures of disease severity or disease activity. However, MRI appears to be predictive of response to therapeutic interventions such as intravenous pulse corticosteroids, orbital radiotherapy and cyclosporine. In one study, MRI T2-relaxation had a 64% positive predictive value and a 92% negative predictive value for the response to orbital radiotherapy as subjectively reported by the patient and managing physician. Response to treatment included improvement in diplopia, proptosis and soft-tissue swelling.

The role of gadolinium enhancement of EOM's in fat-suppressed T1-weighted images is more controversial. The literature depicts mixed results with both increased and decreased enhancement described in active and post-treatment TED. These studies are also limited in size and differed with regards to TED disease activity. A systematic evaluation of EOM enhancement and multiple measures of disease activity is needed to determine the utility of this measure in TED.

Finally, STIR (short tau Inversion recovery), modified to control for variation among scanners using a ratio of orbital tissue brightness compared to the ipsilateral temporalis, but then abandoned in favor of evaluating chemical shift fat-suppressed T2-weighted images. In addition, the STIR sequence is not a quantitative measure of T2 relaxation times or abnormal signal.

The use of prolongation of T2 relaxation times to identify extraocular muscle edema is the technique that has been the most widely studied, appears likely to be the most specific and has the fewest technical difficulties for a multi-center trial.

REVIEW OF CLINICAL STUDY PLANNING PROJECT AND PILOT STUDIES PROGRESS

Our review of previously published evidence suggests the need to **develop, confirm and validate measure(s) of TED disease activity.**

1. The use of a **clinical assessment tool** for identifying active disease, grading its severity, and documenting its progression (VISA).
2. The use of validated **standard external photographs** for improving reproducibility of disease grading.
3. The use of a validated **quality of life questionnaire** for examining impact of pain, disability, and disfigurement on visual function and social interactions in patients with TED.
4. Testing serum and plasma for thyroid function and the presence of markers of autoimmunity including TSI, TRAB, c-reactive protein, and fibrocyte index as objective markers for disease activity, severity and progression.

FUTURE THERAPEUTIC ARMS OF TEDTT MAY INCLUDE

1. Corticosteroids
2. Anti B cell agent (Rituxamab)
3. Anti T cell agent (anti-CD3)
4. IL-1 neutralizing antibody

CME ANSWERS

1. Active thyroid eye disease patients have redness, fluid accumulation and occasionally pain that fluctuates over the course of the day and day to day.
2. Serum markers, urine markers, MRI, and ultrasound are four examples.
3. Thyroid stimulating immunoglobulin can be a helpful adjunct and is widely available.

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SURGICAL TECHNIQUES FOR ANATOMIC RESTORATION

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LEARNING OBJECTIVES

1. List the 4 stages of surgical rehabilitation of anatomic function.
2. Discuss surgical considerations for each of the 4 stages.
3. Discuss potential surgical approaches for decompression surgery.

CME QUESTIONS

1. The decompression procedures least likely to cause diplopia:
 - a. Fat decompression
 - b. Lateral wall bone removal
 - c. Medial wall decompression
2. List 4 stages of surgical rehabilitation in order of approach.
3. List three possible complications of orbital decompression surgery.

KEY WORDS

1. Thyroid Associated Orbitopathy
2. Graves' Disease
3. Orbit
4. Decompression surgery
5. Management

NATURAL HISTORY AND PATHOPHYSIOLOGY OF TED

Graves's disease is a systemic autoimmune disorder encompassing the thyroid, orbit and connective tissues. The orbital manifestations are termed Thyroid Eye Disease (TED) and occur in up to 50% of patients, but <5% of the cases are vision threatening. The pathogenesis of TED is complex but includes early immune infiltration and expansion of the orbital connective tissues. The orbital fat and extraocular muscles are most prominently affected and expansion of these components can cause significant impairment.

The pathogenesis of TED appears to target the fibroblasts within the connective tissue. Orbital fibroblasts from TED

patients have a central role in disease development due to several unique attributes. They profoundly induce inflammation, extracellular matrix production and fibrosis.

OVERVIEW OF SURGICAL CONSIDERATIONS

Except to treat optic neuropathy, surgical techniques have been largely utilized once the inflammatory phase subsides. These techniques alleviate the consequences of volume expansion and soft tissue infiltration associated with TED.

Several considerations are critical when evaluating patients for surgical treatment. Since TED is a heterogeneous disease which affects people with disparate facial anatomy, it is critical to outline an individualized paradigm for patient assessment and treatment planning.

A primary clinical consideration for treatment planning is assessment of disease severity. This assessment is multifold and includes clinical symptoms such as eye pain from exposure, retrobulbar pressure and includes severity of change from the premorbid state. While exophthalmos measurement is important, patients with varying degree of proptosis will exhibit diverse symptoms. Degree of proptosis should be considered in light of racial differences and norms. For example, patients with congenital maxillary hyperplasia have relatively prominent globes at baseline and further expansion can often lead to decompensation. In contrast patients with deep set globes may notice significant differences in their facial appearance, but signs of lagophthalmos and exposure keratopathy will often be limited. Old photographs from the previous 5–10 years are a routine part of a complete baseline examination. Photos are critical to assess the severity of transformation and are the basis for demonstrating these changes and possible treatment options.

Identification of poor surgical candidates is complex and can take many forms. Understanding a patient's objectives and desires is critical and can often require several detailed meetings. TED surgery is strenuous for the patient due to the multiple stages required and the anticipated complexities. Patients who are not committed or enthusiastic to endure this process become easily disenchanting. For these patients, medical support and camouflage techniques which are less invasive are often better tolerated. Other patients who may be poor candidates include patients with underlying medical issues such as hematologic or bleeding problems. Since fibrosis

can be complex in this disease, excessive bleeding can limit surgical options. While patients at any age can consider surgery, after age 60 I think twice about it but proceed if no contraindications. After age 70, my personal management becomes more conservative and shifts largely to camouflage techniques if possible.

SURGICAL STAGES OF RECONSTRUCTION

There are four stages of anatomic restoration for TED patients. However it is critical to maximize medical management of dry eye and lagophthalmos. All four phases of reconstruction are considered and discussed with each patient to provide an overview of the strategy. Classically orbital decompression surgery is considered initially, followed by strabismus surgery, eyelid surgery and finally aesthetic–functional surgery. In addition, no surgical camouflage techniques are available during any phase of reconstruction and include use of Botulinum toxin and hyaluronic acid fillers. These agents are often critical to provided aesthetic functional improvements which provide encouragement while undertaking this process. Botulinum toxin can relieve the discomfort associated with excessive corrugators use in response to lid retraction and exposure keratopathy. Hyaluronic acid fillers can offer dramatic improvement of eyelid contour and height abnormalities in addition to cheek and midface enhancement and reduce lagotophthalmos. Fillers placed at the levator aponeurosis can reduce eyelid retraction thus fine tuning eyelid height by 1–2 mm.

DECOMPRESSION SURGERY

The first surgical consideration is whether a decompression is needed to restore function. The basis for this evaluation is complex and not solely based upon proptosis measurements. A patient's symptoms and signs, expectations, disease type (fat or infiltrative) and current level of dysfunction are critical considerations.

Decompression surgery is tailored to each patient's unique circumstances. Graded decompressions can range minimally invasive fat removal under local anesthesia achieving a 2–3 mm reduction in proptosis to multiple wall bony removal reserved for patients with aggressive and severe disease. Thus no one decompression fits all patients.

A patients starting globe position can be assessed from old photographs and will provide clues to the patient's perceptions regarding the changes in their physical features. Patients will most often seek a return to their premonitory appearance and this possibility can be openly discussed in terms of risk versus reward.

The presence or absence of restrictive extraocular motility and diplopia is an important consideration for surgical planning. Diplopia is a severe impediment to daily activities, thus minimally invasive procedures or limited decompressions involving fat removal and lateral wall removal are more attractive in patients without

preoperative diplopia. These procedures typically have substantially less risk of postoperative diplopia. Patients will often accept less decompressive effect to avoid the potential complications of diplopia. In contrast patients with infiltrative disease and preexisting double vision may benefit from decompression surgery which alleviates the congestive effects of the disease. Since strabismus surgery would be addressed regardless, the benefit of addition decompress is more convincing.

TECHNIQUES AND APPROACHES

Decompression Surgery

Decompression techniques have evolved over the last several years, shifting toward surgical procedures which have less morbidity. Soft tissue or fat decompressions have gained popularity given the relatively low complication rate. Fat decompression can be performed in isolation or in conjunction with a bony decompression. Intraconal orbital fat can be readily obtained from the inferolateral or inferomedial quadrant with minimal risk to adjoining structures. Superolateral and superomedial fat removal is also possible though this area is highly vascular and surrounds the lacrimal gland and trochlea. Intraconal fat removal is ideal since removal of blepharoplasty fat can cause inferior eyelid and cheek hollowness which may cause increased inferior scleral show and worsen the appearance.

It is critical to avoid aggressive pulling of orbital fat and to identify fat prior to excision. Homeostasis is critical but indiscriminate use of cautery can be more deleterious. Use of a Frazier suction tip to “grasp” the fat can be useful when the fat is “woody” or highly fibrotic. Patients with muscle infiltration and expansion have orbital congestion which complicates hemostasis. Despite limited apparent fat volumes, these patients often demonstrate a substantial incremental effect of fat removal.

Expectations for fat removal are typical 2–3 mm. Measuring the fat volume removed will allow standardization of surgical technique. One can expect an 1 mm reduction in proptosis for each 1 cc of fat removed. Development of new onset diplopia in patients undergoing fat decompressions is approximately 1–2%.

Lateral orbital decompression with removal of the greater wing of the sphenoid and posterior face of the zygoma provides substantial proptosis reduction. The surgical approach can be from the eyelid crease or through the lower eyelid with a swinging eyeing flap. The upper eyelid approach is elegant and does not require reconstruction or reapproximation of the canthus. The dissection to the lateral orbit is a subperiosteal approach which exposes the bone from the superior orbital fissure to the inferior orbital fissure. It is critical to elevate the periosteum and lateral canthal attachments from the bone (in a subperiosteal manner) in addition to releasing the attachments from the anterior face of the sigma. This dissection will achieve maximal visualization of the lateral bony structures. A superior lateral notch is created using a

high-speed drill with a 3mm diamond dusted cutting burr providing direct access to the lateral orbit. Bone removal begins at the junction of the zygoma and frontal bone and progressing to the superior orbital fissure and then toward the inferior orbital fissure. Areas of diploë bone are removed during this process. In addition the posterior face of the zygoma can be thinned providing substantial bony removal.

There are several important caveats during lateral decompressions. First, homeostasis is critical and a diamond dusted burr will aid homeostasis due to the coagulating nature of the tip. In addition, a curette can be used to remove bone from the diploë since drilling in this area is difficult since visualization is often compromised. Also uniform removal of bone is the goal and avoids forming a trench of bone which may not allow expansion of orbital contents.

In this same regard, the periosteum must be completely opened allowing the orbital contents to expand completely into the newly created orbital space. If the periosteum is not completely opened at the apex, it will tent the area of decompression and not allow volume expansion.

In general, lateral decompression can provide 3–6 mm of overall proptosis reduction. The overall risk of double vision is approximately 5–10% but varies with patient presentation and degree of bone removal.

Additional bone decompression techniques include a medial approach to facilitate ethmoid, sphenoid and palatine bone removal. Medial decompressions can be approached through the caruncle and conjunctiva with good exposure for dissection toward the orbital apex. It is necessary to cauterize the anterior and posterior ethmoid arteries to allow posterior dissection. Removal of the posterior ethmoid walls allows substantial apex decompression. Strabismus complications increase with anterior ethmoid removal and is typically avoided. Medial decompressions can provide prompt resolution of optic neuropathy but require substantial comfort with surgical anatomy. Rates of strabismus after medial decompression vary depending upon anterior extent of bone removal and severity of disease but range from 25 to 45%.

Inferior wall decompressions are also considered in patients with substantial proptosis and can be approached with extension of the medial or lateral incisions. Removal of the inferior floor provides substantial decompression but can cause significant hypoglobus, strabismus and torsional double vision. These complications can be minimized to some extent if the anterior 2/3rds of the infraorbital strut is left intact. Strabismus is typically seen in 30–50% of cases.

STRABISMUS AND EYELID SURGERY

The second stage of reconstruction is strabismus evaluation and correction. Typically surgical technique utilizes muscle recessions and adjustable sutures although individual preferences and circumstances are widely variable.

The third stage of reconstruction is eyelid reconstruction and can be divided into upper or lower eyelid dysfunction. TED causes substantial upper eyelid retraction due to the fibrotic infiltration of the levator and Muller's muscles. The goal of upper eyelid surgery is to lower the eyelid while maintaining a normal appearing contour and reducing lateral flare. Lateral flare of the upper eyelid is a tell-tale sign of TED. Since the overall eyelid height can vary greatly in TED patients, it is important to assess the height and amount of lateral flare at rest, during conversation and in photos. Many patients proficiently reduce their eyelid height in photos but demonstrate not in casual or animated conversation.

Surgical approaches to lower the eyelid height or contour include lengthening the levator–Muller's muscle complex. While ptosis surgery can be unpredictable, TED eyelid surgery is even more frustrating since there can be substantial return of eyelid elevation with postoperative healing and scar formation. Multiple procedures are often needed and patients should be counseled prior to surgery.

Lower eyelids position can also be compromised in patients with TED due to the relative prominence of the globes or previous surgery. Surgical and non surgical options are available depending upon the degree of eyelid retraction and complexity of fibrosis on upward eyelid testing. A diverse array of procedures is available, but individual patient considerations are important. One must consider whether there is substantial cicatricial volume collapse, globe prominence etc to properly choose surgical approaches. Cicatricial eyelid retraction results from a combination of relative volume loss and fibrosis. Surgical approaches include placement of a stent, recessing the lower eyelid retractors from the tarsus. It is critical to consider use of antimetabolites in these cases to minimize fibrosis.

Volume augmentation is another useful adjunct to support the lower eyelid. Hyaluronic acid or fat can be used and each has their own distinct advantages and disadvantages. Bony midface support is also critical in the context of relative globe prominence. If additional decompression is not possible, bony midface augmentation with fillers or onlay implants could be considered.

In general, procedures such as lateral canthal tendon shortening and tarsorrhaphy are usually not indicated and will often complicate the situation, provide little improvement or be aesthetically displeasing.

AESTHETIC RECONSTRUCTION

The final stage of the reconstructive process is facial aesthetic reconstruction. Despite the best surgical efforts described above, patients will often complain that their appearance has significantly changed. This likely stems from the fact that TED affects tissue in the periorbit, midface and eyebrow region. Thus targeting these areas are critical to complete restoration of function.

Eyebrow prominence and corrugator muscle over-action are profound by many patients. Noninvasive approaches such as Botulinum toxin to the corrugator muscles can help immensely, but often additional measures such as brow lifting and blepharoplasty are required. The brow fat pad of TED patients can be sculpted to create a less prominent appearance. In addition endoscopic brow surgery can be very beneficial when combined with corrugator muscle removal or weakening.

There is often substantial midface and cheek expansion with malar fluid accumulation and can create a prominent appearance to the upper face. Adding volume to the lower face and nasolabial folds can balance this appearance. Review of old photographs demonstrating facial and cheek prominence will assist placement. In addition, lower eyelid fat prominence can be reduced with targeted blepharoplasty and or filler placement. Care should be taken prior to face-lifting procedures since many patients are susceptible to increased fluid accumulation especially in the malar triangle which can be exacerbated by face lift procedures.

CME ANSWERS

1. A
2. First decompression, strabismus surgery, lid procedures, aesthetic rehabilitation
3. Many but include pain, double vision, numbness, and vision loss.

OCULAR MOTILITY IN THYROID EYE DISEASE — EVALUATION & SURGERY

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LEARNING OBJECTIVES

1. Understand the underlying pathology of Thyroid Eye Disease.
2. Know the techniques for quantitatively evaluating extraocular motility in a patient with Thyroid Eye Disease.
3. Understand the options for medical and surgical management of double vision in patients with Thyroid Eye Disease.

CME QUESTIONS

1. What is the underlying pathology affecting the extraocular muscles in Thyroid Eye Disease?
2. Name three different techniques for performing extraocular muscle surgery on patients with Thyroid Eye Disease.
3. What is the recommended time interval for stability of motility findings prior to considering extraocular muscle surgery? What are some exceptions?

KEYWORDS

1. Graves' Disease
2. Thyroid Eye Disease
3. Ocular Motility
4. Diplopia
5. Extraocular Muscle Surgery

INTRODUCTION

Evaluation of diplopia in the patient with Thyroid Eye Disease requires differentiating between monocular and binocular diplopia, both of which may occur. The aetiology of binocular diplopia relates to the extent of muscle fibrosis secondary to an inflammatory process that may have both autoimmune and ischemic components. There are many methods for measuring motility limitation and assessing binocular misalignment. Medical management may include occlusion, Fresnel, and ground-in prism. Stable measurements are necessary in most instances to maximize surgical outcomes. Surgical management techniques vary, and may include either fixed or adjustable sutures, duction based or misalignment based determination of the amount of surgery required.

MONOCULAR AND BINOCULAR DIPLOPIA

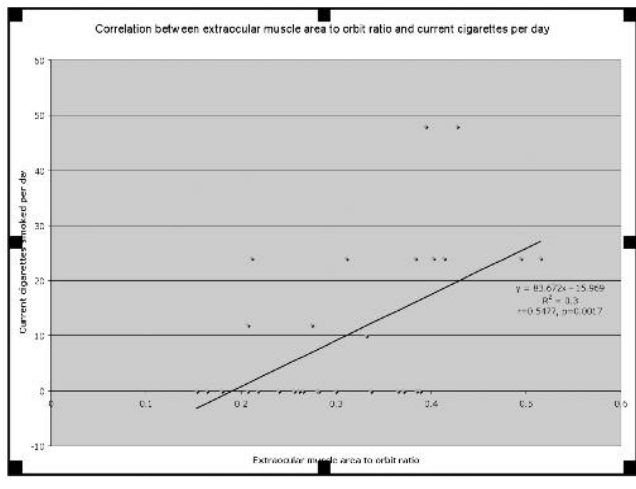
Patients with Thyroid Eye Disease (TED), previously referred to as Graves' Ophthalmopathy or Orbitopathy, frequently complain of diplopia. The diplopia can either be monocular or binocular. Common causes of monocular diplopia include corneal astigmatism, corneal surface irregularity, or macular disease. Corneal astigmatism may be the result of abnormal eyelid position, either retraction or ptosis¹⁻⁵. It can also result from contracture of a rectus muscle, inducing astigmatism⁶. Dry eye or corneal exposure with epithelial disease may be responsible for corneal surface changes. Orbital pressure on the globe, deformity of the posterior globe from an enlarged rectus muscle belly, or both may be responsible for distortion of the macula⁷.

Binocular diplopia occurs when there is asymmetric restriction of the extraocular muscles. Usually the inferior rectus muscles are involved first, followed by the medial, superior, and lateral recti in order of both frequency and severity⁸. Binocular diplopia may also be caused by associated ocular myasthenia gravis⁹⁻¹¹, which may affect up to 0.2% of individuals with Graves' Disease. Of patients with myasthenia gravis, 5% may develop Graves' Disease.

ETIOLOGY OF BINOCULAR DIPLOPIA

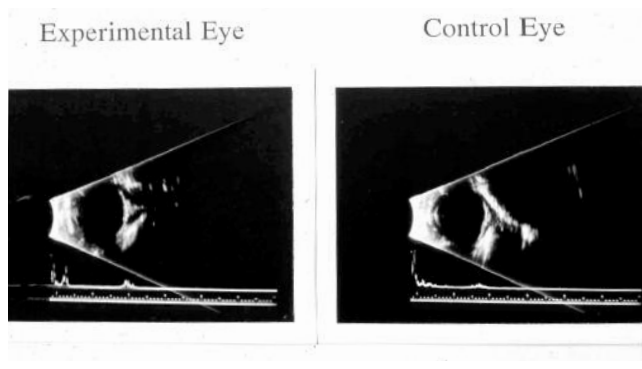
The restrictive muscle disease results from changes within the extraocular muscles, including round cell infiltration, glycosaminoglycan (GAG) deposition, edema, fibroblast proliferation, and fibrosis¹²⁻¹⁴. In a recent retrospective study of patients at the Flaum Eye Institute in Rochester, we correlated the relative size of the extraocular muscles on coronal imaging to daily amount of cigarette smoking and found a highly significant positive correlation (unpublished data, Figure 1).

FIGURE 1: The ratio of muscle area: orbit area on CT coronal section increases significantly with the number of cigarettes smoked per day.



Venous obstruction from elevated intraorbital tissue pressure, venous outflow obstruction, or a combination may contribute to the inflammatory response. Saber and Feldon¹⁵ demonstrated infiltrative extraocular muscle disease with increased cross-sectional muscle diameter on ultrasound (Figure 2), and restriction quantified by length-tension curve assessment, using a cat model.

FIGURE 2: In a cat model of orbital venous outflow obstruction (left), b-scan ultrasound shows increase in muscle thickness compared to control (right).



EVALUATION OF BINOCULAR DIPLOPIA

In approaching the motility evaluation of the TED patient, assessment of spontaneous head position is important. Commonly, patients with tight inferior rectus muscles adopt a chin up position, even if they have no subjective complaints of diplopia. A tight medial rectus muscle may result in a head turn to minimize diplopia. These preferred head positions may substantially affect quantitative measurements of ocular misalignment, measured by Krinsky light reflex, Maddox rod, Lancaster/Hess screen, or prism correction. Interestingly, the more important measure for assessment of TED motility is duction with maximal patient effort in the horizontal and vertical gaze positions. Assessment can be performed using several

methods¹⁶⁻²⁰, including estimations using the light reflex, Goldmann bowl, or movement relative to the palpebral fissure. The limitation can be expressed in semi-quantitative terms (none, mild, moderate, severe) or in degrees expressed numerically or as a percentage with the patient looking up, down, left, and right.

MANAGEMENT OF BINOCULAR DIPLOPIA

Occasionally, diplopia may only be present in the early morning. Although this may be due to disassociation of a phoria from sleep, it is often related to increased orbital edema with the patient lying flat. Elevating the head of the bed on blocks and/or adding a diuretic may be helpful in eliminating transient morning double vision. Even when patients have constant diplopia, the amount may vary during the progressive phase of the disease. Depending upon the rate of change (hours, days, or weeks), Fresnel prisms or monocular occlusion may be indicated. Once the diplopia has stabilized, it may be concomitant, unvarying with eye position, or non-concomitant, changing measurements with change in gaze position. Concomitant deviations can be managed with Fresnel or ground-in prism in spectacles, if the deviation is small. However, if the deviation is large or the deviation is non-concomitant, then extraocular muscle surgery is often necessary to restore binocularity.

SURGICAL MANAGEMENT OF BINOCULAR DIPLOPIA

Surgery on the extraocular muscles may be considered to eliminate double vision, eliminate abnormal head position, or both. In general, muscle surgery should not be considered unless the measured motility duction and versions are unchanged for a minimum of 6 months. Occasional exception does occur, such as requirement for binocularity to work or orthopedic issues related to head position. I find testing to determine the area of binocular fusion that can be achieved using prisms. Such information helps to predict whether the patient is likely to have a useful area of single binocular vision post-operatively even if substantial phorias remain in different positions of gaze.

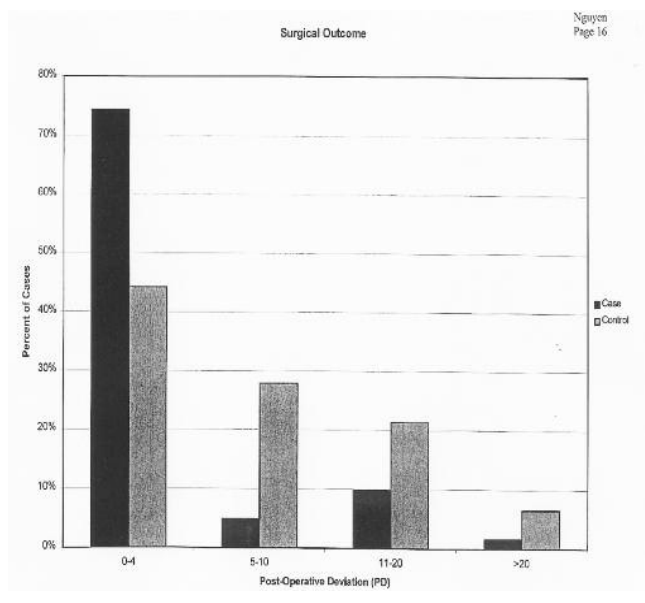
Contradicting opinions have been published regarding the use of orbital decompression to improve outcomes of extraocular muscle surgery in TED patients. Those who advocate pre-operative decompression suggest that reducing proptosis improves the length-tension curve of EOM and reduces the incidence of late overcorrection. Of course, if orbital decompression is contemplated regardless of motility, it should be done first, as motility is likely to change after decompression due to changes in the muscle position relative to the eye position within the orbit. Those who argue against decompression prior to muscle surgery believe that moving muscles into non-physiologic positions increases overall restriction and changes the direction of muscle forces on the globe. In an unpublished retrospective study, we found that patients

undergoing decompression prior to muscle surgery required more muscle surgeries and had a higher incidence of persistent diplopia.

SURGICAL TECHNIQUES FOR BINOCULAR DIPLOPIA

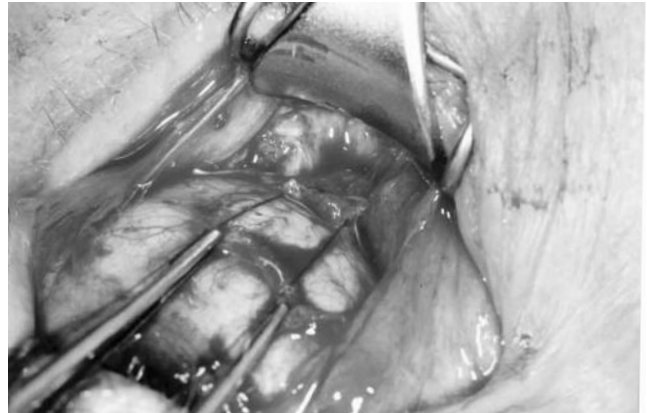
The mainstays for extraocular muscle surgery in TED patients are fixed and adjustable suture recessions of restricted muscles. Varying success rates have been reported for both of these procedures²¹. Most series are relatively small, though Dyer²² reported a 45% re-operation rate for fixed recessions in 116 patients. Although re-operation rates were as low as 17%–25% in small series, problems with adjustable recessions include patient discomfort (or intolerance) and a tendency toward late overcorrection²³.

FIGURE 3: Percentage of patients with excellent realignment of eyes is much higher in patient group treated using release of restriction method (dark bars) compared to usual realignment technique of eye muscle surgery



Both vertical and horizontal misalignments occur, either separately or together in the same patient. In trying to determine predictors of large vertical deviations, Prendiville, et al²⁴ found that restriction asymmetry was the best predictor and that very large hypertropias were associated with restriction of the contralateral opposing rectus muscle.

FIGURE 4: Surgeon’s view of eye moved into full supraduction after detachment of the inferior rectus muscle. Muscle is stretched across sclera to identify amount of recession required to alleviate the restriction.



Another controversy that has developed in the literature is whether correction goals during surgery should be based upon correcting the misalignment or correcting the restriction of each extraocular muscle independently. Feldon first reported the release of restriction as an improved method for determining the amount of recession, improving success of primary surgery from 44% to 74%²¹. In Figure 3, the histogram demonstrates a higher percentage of patients with better alignment using the release of restriction method compared to using the binocular re-alignment method. The technique is illustrated in Figure 4, showing the eye placed at the point of maximum excursion with the muscle stretched onto the sclera to define the amount of recession. A similar technique was later published by Dal Canto et al²⁵. Cruz found no difference in outcome between the two methods²⁶.

Often, extraocular muscle surgery is only partially successful in restoring binocularity in patients with TED. Large concomitant deviations usually require addition rectus muscle recessions. However, inferior oblique recession has been suggested by Newman (presented at AOS, 2009). Small deviations or deviations only in eccentric gaze positions may benefit from Z-myotomy, Faden posterior fixation procedure, and even muscle resection.

SUMMARY

In conclusion, outcomes for ocular misalignment in patients with TED may be enhanced using the following suggestions:

1. Measure both the deviation and the restriction.
2. Allow as much time as possible for misalignment to stabilize.
3. Consider planning surgery to relieve restrictions rather than to correct the amount of deviation. This will decrease dependency on adjustable sutures.
4. For large deviations, evaluate and relieve contra lateral opposing restriction.
5. Perform orbital decompression only if there are indications other than motility.
6. Forewarn your patients that the overall reoperation rate is at least 25–30% in the most experienced hands.

CME ANSWERS

1. Infiltration of the extraocular muscles with round cells, glycosaminoglycans and fibroblasts.
2. Fixed suture technique, adjustable suture technique, alleviation of restriction technique.
3. 6 months, but may be earlier if required for patient to work or if there are orthopedic issues due to abnormal head position.

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