Thyroid Eye Disease: Overview and Treatment

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Your immune system consists of a guided molecular army of antibodies equipped to recognize millions of foreign enemy antigens. However, in autoimmune conditions, antibodies are produced which target the cells of your own body. This is how many autoimmune diseases begin, including thyroid eye disease.

Thyroid eye disease (TED) is a rare autoimmune orbitopathy, or disorder of the orbital cavity, characterized by tissue inflammation, expansion, and fibrosis that may be potentially vision-threatening. It takes many names including "Graves' ophthalmopathy" and "Graves' orbitopathy" (GO) since approximately 90% of cases are associated with hyperthyroidism caused by Graves' disease.[1] However, it is also known more generally as "thyroid-associated ophthalmopathy" and "thyroid-associated orbitopathy" (TAO) since about 10% of patients are in a euthyroid state or have hypothyroid chronic autoimmune thyroiditis.

By an autoimmune mechanism not yet clearly understood, TED begins with the production of antibodies which specifically target and activate thyroid-stimulating hormone (TSH) receptors.[2] As one would expect, these receptors are located on the cells of the thyroid gland. When bound excessively by these autoantibodies, thyroid follicular cells are stimulated, increasing the production and release of thyroid hormone and causing the classic clinical picture of hyperthyroidism. However, these TSH receptors are also found on cells in the orbit! In particular, they are found on orbital fibroblasts and adipocytes. Moreover, there is an overexpression of these TSH receptors in the retrobulbar tissue of patients with Graves' hyperthyroidism compared to controls.[2] TED pathophysiology unfolds as antibody binding causes activation of CD4+ helper T cells, which infiltrate the tissue and release cytokines, leading to a local inflammatory response. This stimulates the fibroblasts, causing them to proliferate, secrete extracellular matrix material called glycosaminoglycans (GAGs), and differentiate into adipocytes. The GAGs produced, including hyaluronic acid, create a hyperosmolar environment which draws intracellular and intravascular fluid into the orbit's contents including the extraocular muscles and the levator palpebrae muscle. Overall, this ensuing inflammation leads to an increased volume of orbital connective tissue, fat, and muscle in the tightly packed orbital space (**Figure 1**).

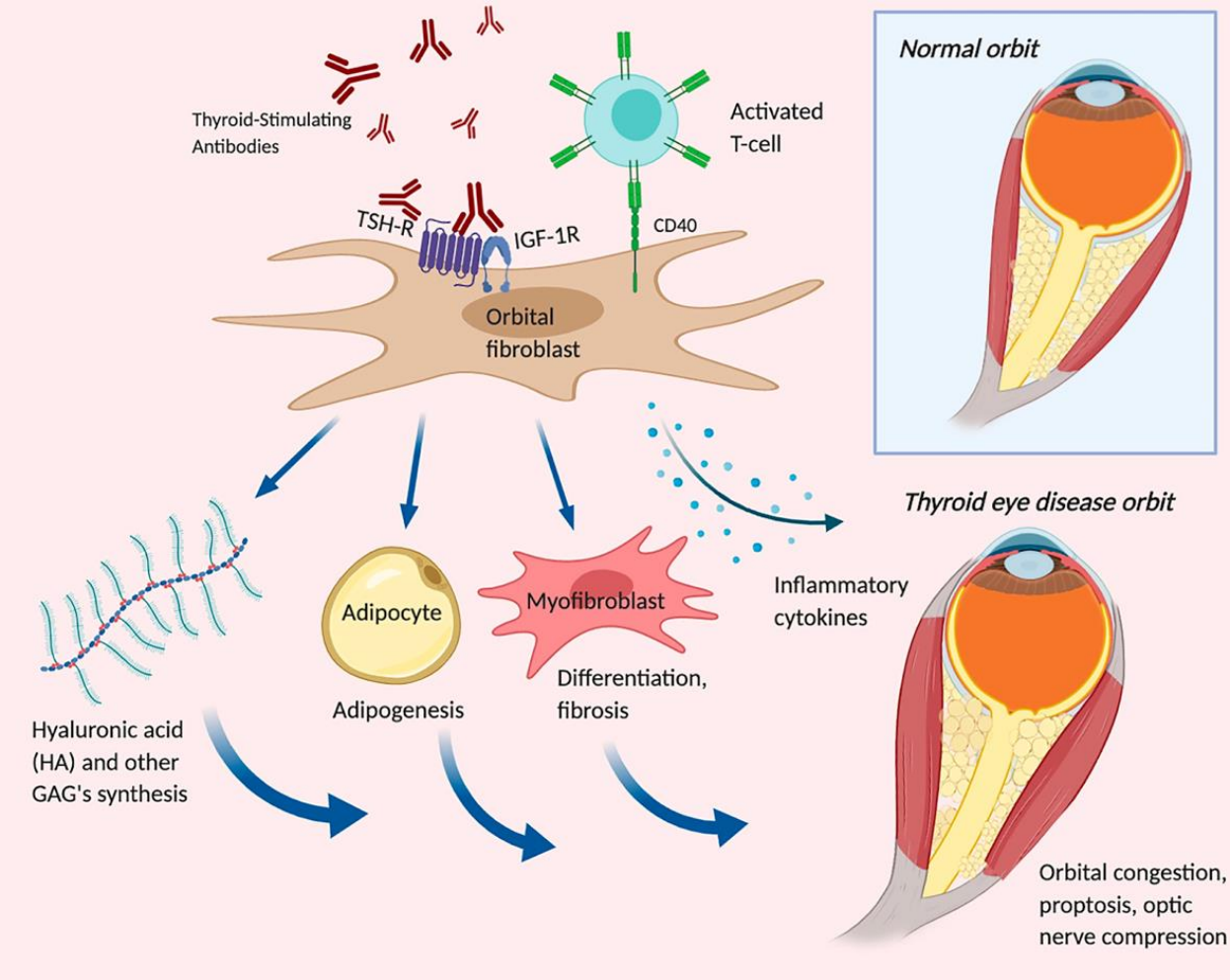

Figure 1. *Pathophysiology of TED begins with binding of autoantibodies to TSH receptors on orbital fibroblasts.*[3]

With this swelling and added volume, the pressure in the 30-milliliter orbital cavity increases until the mobile globe of the eye, or eyeball, has to give. Following the path of least resistance, the globe is pushed forwards, causing a "bulging eye" appearance. This phenomenon can be described by the medical term *proptosis*, which describes any organ that is displaced forward, and even more specifically by the term *exophthalmos,* which refers to the forward displacement of the eyes in particular (**Figure 2**). The exophthalmos is usually bilateral, although it can present more predominantly in one eye than the other. The extraocular muscles may be compressed or swollen unequally causing ocular pain and ophthalmoplegia, or the inability to converge eyes, diplopia, and difficulty reading. Additional symptoms of TED include: upper eyelid retraction from increased sympathetic stimulation of Müller's muscle by thyroid hormone; conjunctival injection and chemosis from

inflammation; and a "gritty" or foreign body sensation, tearing, or blurriness from dryness resulting from failure of eyelids to fully close.

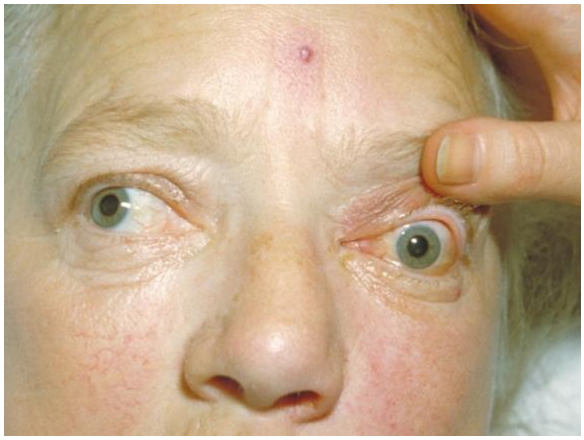

Figure 2. *Bilateral exophthalmos (CDC/Dr. Sellers/Emory University).*[4]

In the majority of patients, untreated TED follows the Rundle's curve of disease progression (**Figure 3**).[5] This depicts TED as having two phases: 1) an active, inflammatory phase lasting 6 months - 2 years that is also called the dynamic phase, in which disease progression occurs and 2) an inactive, post-inflammatory phase that is also called the stable, static, or quiescent phase, in which disease progression had halted leaving the symptoms of tissue damage and gradually improving motility to a plateau.

However, in <5% of patients with TED, an ocular emergency may develop called compressive optic neuropathy (CON), as compartment syndrome occurs at the apex of orbit and compresses the optic nerve. This decreases vision, color vision, contrast sensitivity and relative afferent pupillary defect. The characteristic visual fields commonly show central, cecocentral, paracentral, and nerve fiber layer bundle defects. Optic nerve head examination can be normal, optic disc edema, or pallor.

An important note to make here is that smoking is the most consistently linked risk factor to the development or worsening of TED. Thus, smoking cessation counseling is an important part of treatment. As TED is self-limiting, treatment of the majority of cases consists of conservative local measures such as eye protection and sleeping with the head of the bed elevated, as well as maintaining a euthyroid state which prevents worsening TED. In moderate to severe disease, corticosteroids may also be used to reduce GAG production and swelling in the orbital cavity. Exciting developments have been made in TED treatment in recent years. Teprotumumab was FDA-approved in 2020 for TED and is now considered first-line for moderate to severe disease.[6]

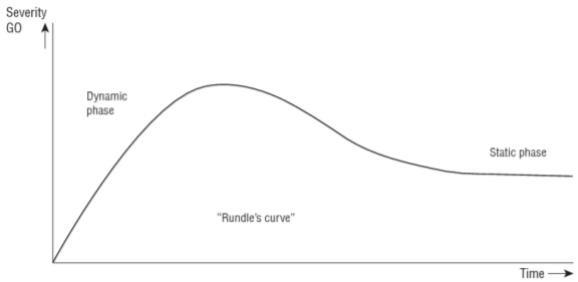

Figure 3. *TED progression follows Rundle's curve.*[5]

Patients who do not respond well to treatment may also consider a surgical intervention called orbital decompression surgery which partially sculpts the bony walls of the orbit and thus enlarges the

existing space of the orbit to accommodate for the increased tissue volume. It commonly involves the orbital floor, medial wall, or lateral wall. In rare cases the roof of the orbit may also be decompressed surgically.

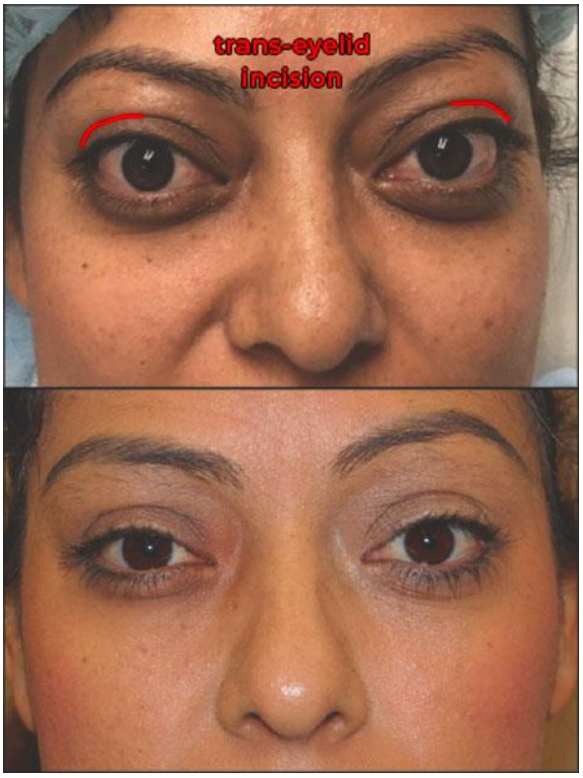

Figure 4. *Transorbital decompression surgery technique via incision through the eyelids.*[7]

Dr. Sathyadeepak Ramesh is a nationally recognized, board-certified oculoplastic surgeon at the Wills Eye Hospital who informed the writing of this article. He trained in oculofacial, orbital, cosmetic, and reconstructive surgery at the Jules Stein Eye Institute at the University of California Los Angeles, where he became an expert in the transorbital techniques of orbital decompression. Dr. Ramesh chooses a trans-eyelid or scarless approach and focuses on moving the eyeball directly back, rather than to the sides, up, or down (**Figure 4**). This reduces the risk of double vision after surgery and increases the power of the surgery. Dr. Ramesh often combines this technique with fat removal or sculpting to address areas of fatty enlargement in the brows, cheeks, or eyelids, or additional cosmetic procedures such as eyelid lifting, eyebrow lifting, or facial fat injections. This elegant combination of techniques allows Dr. Ramesh to deliver consistent and aesthetically pleasing results in these complex cases. Because of refinement of his technique, he can perform this surgery for milder disease or even purely for cosmetic benefit.

References

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