# *Dysthyroid Ophthalmopathy and Related Immunological Disorders*

## Essay

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# *Abstract*

The immune system does not normally recognize and respond to self antigens, this is due to its ability to differentiate self from non-self antigens, known as self-tolerance. Autoimmunity occurs when there is a failure in the normal mechanism of self-tolerance. This autoimmune reaction is dependent on the presence of cytokines eg. TNF-α and the presence of adhesion molecules eg. VCAM-1.

TED is an autoimmune condition, where T cells and antibodies attack orbital preadipocytes and muscle cells that bear the TSHR protein. It affects the orbital contents including the extraocular muscles and orbital fat. It's the hallmark of Graves' disease. It's characterized by intense inflammation, which includes proliferation and differentiation of fibroblasts to adipocytes, fat deposition and disordered accumulation of GAGs.



**Key Words:**

**Overview on the immune system, Thyroid gland diseases and underlying pathology, Pathophysiology of Thyroid eye disease.**

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# List of abbreviations:

**15-HETE:** 15-hydroxyeicosatetraenoic acid

**AITD:** Autoimmune thyroid disease

**AMA:** Antimicrosomal antibody test, Antithyroid microsomal antibody test

**Anti-NIS:** Anti sodium iodide symporter

**Anti-TPO:** Anti thyroid peroxidase antibody

**APCs:** Antigen presenting cells

**BCVA:** Best corrected visual acuity

**COX-2:** Cyclooxygenase 2

**CSF:** Cerebrospinal fluid

**CT:** Computed tomography

**CTLA-4:** Cytotoxic T- lymphocyte antigen-4

**EC:** Endothelial cells

**FTI:** Free thyroxine index

**GAGs:** Glycosaminoglycans

**GO:** Graves' ophthalmopathy

**HLA:** Human leucocytic antigen

**ICAM-1:** Intercellular adhesion molecule-1

**ICMA:** Immunochemiluminometric assay

**IDDM:** Insulin dependent diabetes mellitus

**IFN- γ:** Interferon-γ

**IGF-1:** Insulin-like growth factor 1

**IgG:** Immunoglobulin G

**IGSF:** Immunoglobulin supergene family

**IL-12:** Interleukin-12

**IL-13:** Interleukin-13

**IL-2:** Interleukin- 2

**IL-4, -5, -6,-10:** Interleukin-4,-5,-6,-10

**IMA:** Immunometric assay

**IOP:** Intraocular pressure

**IVIg:** Intravenous immunoglobulin

**LATS:** Long acting thyroid stimulator

**LATS-p:** Long acting thyroid stimulator -protector

**LFA-1:** Lymphocyte function antigen

**MALT:** Mucosa associated lymphoid tissue

**MG:** Myasthenia gravis

**MHC:** Major histocomptablity complex

**MRI:** Magnetic resonance imaging

**MS:** Multiple sclerosis

**NIS:** Sodium iodide symporter

**PHA:** Phytohemagglutinin

**PPARγ:** Peroxisime proliferator activated receptors

**PPRE:** Peroxisome proliferator response element

**RA:** Rheumatoid arthritis

**RAI:** Radioactive iodine

**RIA:** Radioimmunoassay

**SLE:** Systemic lupus erythematosis

**SLK:** Superior limbic keratoconjunctivitis

**T3:** Tri-iodothyronine

**T3RU:** Triiodothyronine resin uptake

**T4:** Thyroxine

**TALT:** Thyroid associated lymphoid tissue

**TAO:** Thyroid assosciated ophthalmopathy

**TBG:** Thyroid binding globulin

**TBIA:** TSH-binding inhibiting antibody

**TBII:** TSH-binding inhibiting immunoglobulin

**TCR:** T-cell receptor

**TED:** Thyroid eye disease

**TG:** Thyroglobulin

**TgAb:** Anti-thyroglobulin antibody

**TGF-β:** Tissue growth factor β

**TGI:** Thyroid growth immunoglobulins

**Th1:** T helper type 1

**Th2:** T helper type2

**TNF-α**: Tumor necrosis factor-α

**TPO:** Thyroid peroxidase

**TPOAb:** Anti-thyroid peroxidase antibody

**TRAb:** Thyroid stimulating hormone receptor antibody

**TSAb:** Thyroid-stimulating antibody

**TSH**: Thyroid stimulating hormone

**TSHR:** Thyroid stimulating hormone receptor

**TSHRAb:** TSH receptor antibody

**TSI:** Thyroid-stimulating immunoglobulin

**TT3:** Total T3

**TT4:** Total T4

**US:** Ultrasonography

**VCAM-1:** Vascular cell adhesion molecule-1

**VEP:** visual evoked potential

**VLA-4:** Very late antigen-4

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# Introduction

Thyroid-eye disease (TED) ***is*** known as Graves ophthalmopathy, thyroid - associated ophthalmopathy, dysthyroid ophthalmopathy, thyroid orbitopathy , thyrotoxic exophthalmos and other terms .The different terminology is because TED may be associated with hyperthyroidism, euthyroidism or even hypothyroidism[1].

TED is part of an autoimmune process that can affect the orbital, periorbital tissue, the thyroid gland and rarely the pretibial skin or digits. TED may precede, coincide, or follow the systemic complications of dysthyroidism[2].

TED is an inflammatory disease of the orbital tissues; it's attributed to an autoimmune process where both cellular & humoral immunity play a role. The effects of inflammation mediated through cytokine release include proliferation of fibroblasts with increased deposition of extracellular matrix mucopolysacharrides, as well as collagen production, adipocyte differentiation and proliferation resulting in salt & water retention within the orbital tissue consequently edema, enlargement of the extraocular muscles, and increased volume of the orbital soft tissues occur with ensuing exophthalmos and in some patients compression of the optic nerve[3].

The ocular manifestations of TED include eyelid retraction, proptosis, chemosis, periorbital edema and altered ocular motility with significant functional, cosmetic and social consequences. Although most cases of TED do not result in visual loss, TED can cause vision-threatening exposure keratopathy, troublesome diplopia, and compressive optic neuropathy therefore, all ophthalmologists should be able to recognize TED[2]**.**

Women are five times more likely to be affected by TED than men, but this largely reflects the increased incidence of Graves' disease in women. Once someone has Graves' disease, his or her sex has little effect on the risk. TED is clinically evident in 25-50% of patients with Graves' disease and 3-5% of the cases develop severe eye disease. Men older than 60 may be at increased risk of more severe disease[4].

The major clinical risk factor for developing TED is smoking, it increases the risk four times than non-smokers, and it's directly related to the number of cigarettes per day. It also increases the risk for progression of ophthalmopathy after radioiodine therapy[5].

Edema, inflammation and late fibrosis account for the decreased function of the extraocular muscles despite relative preservation of the fibers themselves. The recruitment of T cells to the orbits of these patients may result from the expression of the target of the aberrant immune response in Graves' disease and the TSH receptor in the orbits of patients with TED. The orbital fibroblasts especially those present within patients with TED may be more sensitive to the effects of cytokines accounting for the frequent and relatively selective involvement of the orbit in Graves'disease[6].

Treatment varies according to the present problem. Variable lines of treatment are available including steroid treatment, prisms, radiotherapy as well as surgical procedures for different cosmetic and functional problems such as orbital decompression, extraocular muscle or lid surgery [7].

In a study dealing with immunopathogenesis of the disease, immunosuppressant therapy was evaluated. Treatment with glucocorticoids, non-