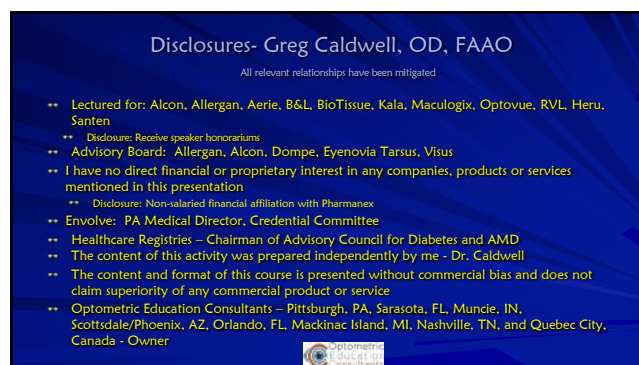
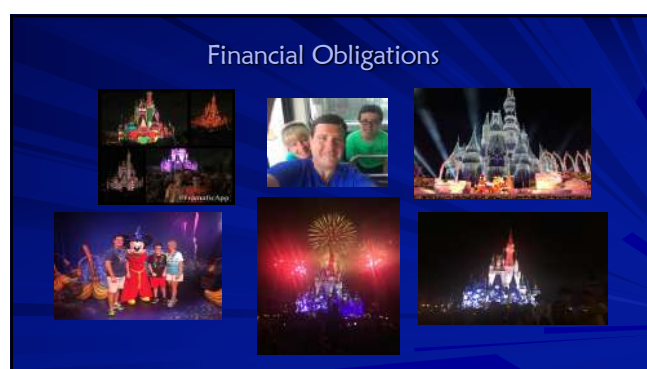


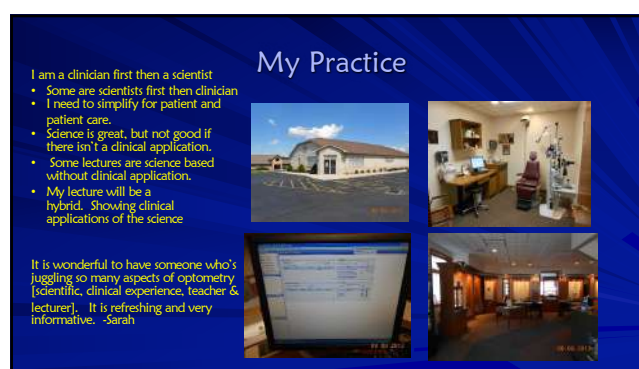
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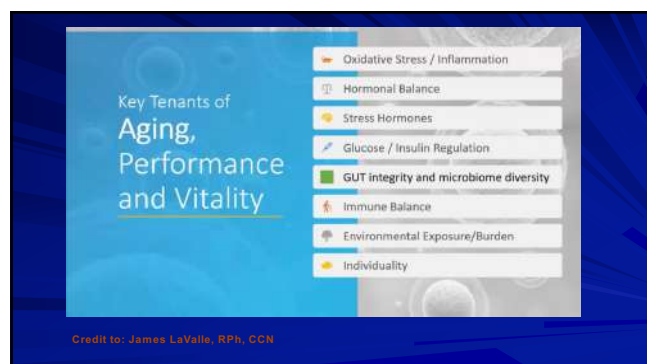
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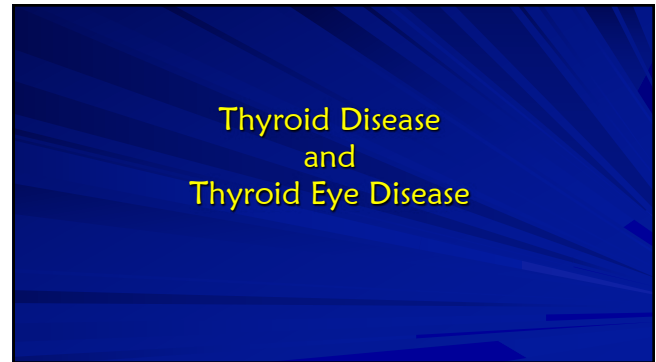
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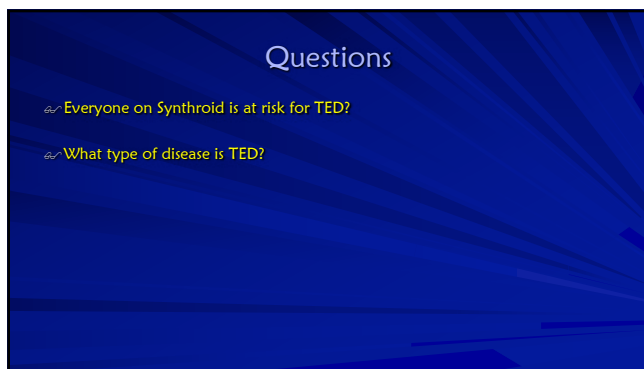
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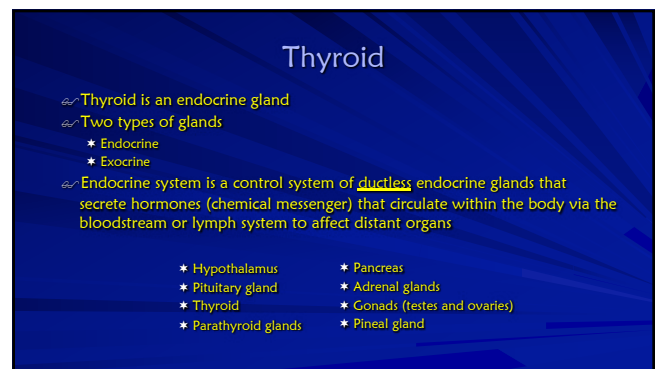
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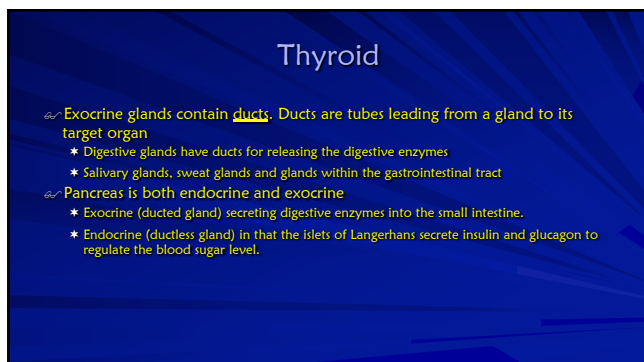
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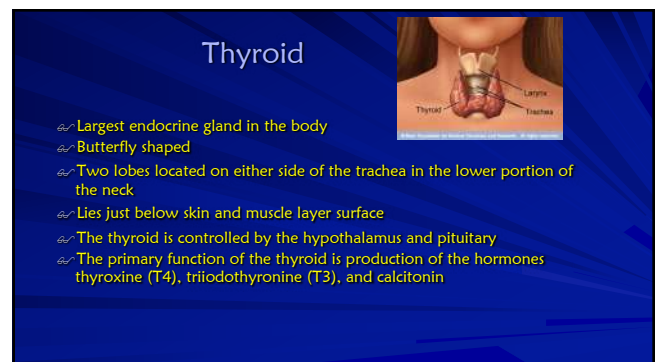
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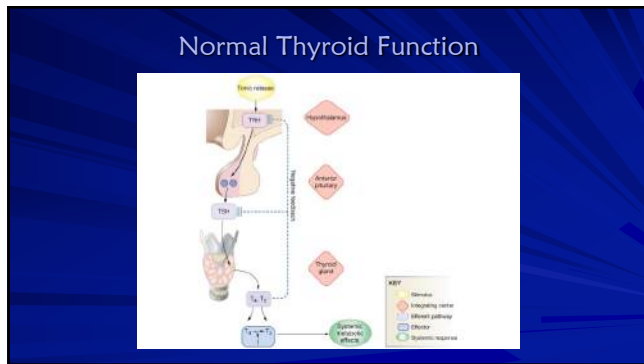
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15

### Thyroid Dysfunction

~ What is the most common cause of thyroid dysfunction?

- Cancer
- Surgically induced
- Medication toxicity or side effect
- Pregnancy
- Autoimmune disease

~ In autoimmune disease the body typically produces \_\_\_\_\_ that attacks itself, this can be systemic or organ specific

- Antibodies, immunoglobulins

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### Thyroid Dysfunction

~ Primary = Thyroid gland

~ Secondary = Pituitary failure

~ Tertiary = Hypothalamic

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### Antibodies of Thyroid Dysfunction

~ TSH Receptor Antibodies

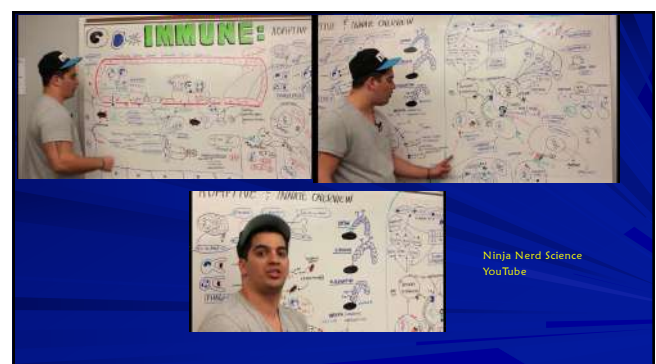
- Stimulating TSH receptor antibody
  - Thyroid Stimulating Immunoglobulin (TSI)
- Thyroid blocking antibody (TBAb)

~ Thyroid Peroxidase Antibodies (TPOAb)

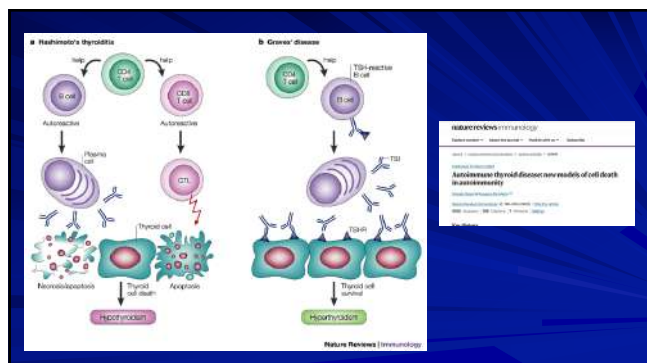
- TPO is found in thyroid follicle cells where it converts the thyroid hormone T4 to T3
- TPOAb contributes to thyroid cellular destruction

~ Most autoimmune thyroid dysfunctions have a combination of thyroid antibodies, however depending on which AB is more abundant results in the outcome of the disease

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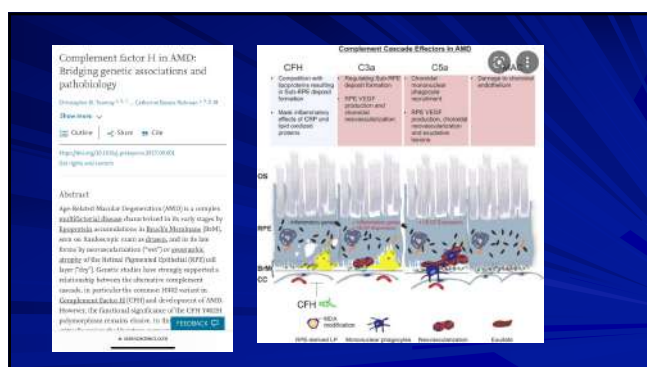
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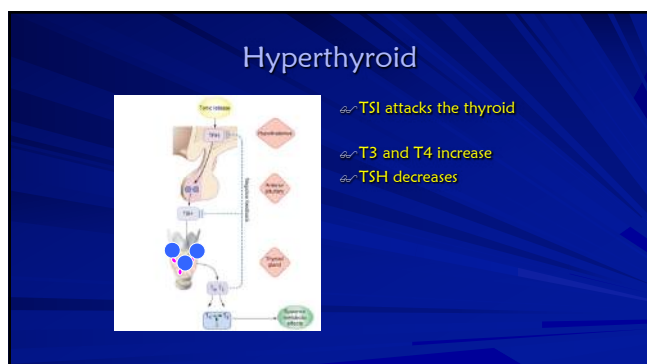
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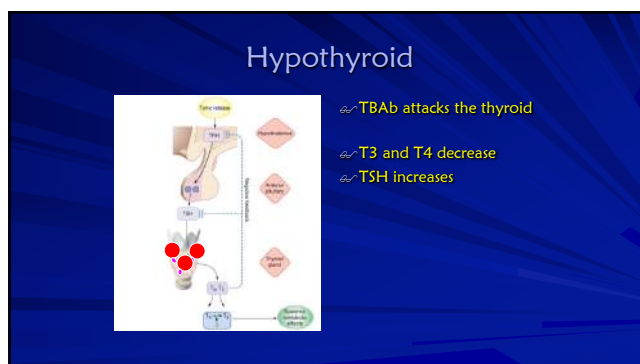
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25



## Thyroid Dysfunction

### Hyperthyroidism

(Thyrotoxicosis)

- ~ Primary-autoimmune
  - \* Graves
    - Graves-Basedow or von Basedow's
- ~ Secondary/Tertiary
  - \* Excess thyroid medication for treatment of hypo or goiter
  - \* Toxic multinodular goiter
  - \* Toxic adenoma
  - \* Excess iodine
  - \* Thyroiditis (inflammatory induced)
  - \* Excess hormone production ectopic tissue
  - \* Thyroid carcinoma

### Hypothyroidism

(most common organ-specific autoimmune disorder)

- ~ Primary-autoimmune
  - \* Chronic autoimmune thyroiditis
    - Hashimoto's thyroiditis
  - \* Autoimmune atrophic thyroiditis
    - Primary myxedema
    - Opposite of Graves disease
  - \* Postpartum thyroiditis
- ~ Secondary/Tertiary
  - \* Lithium medication
  - \* Pregnancy
  - \* Surgically induced
  - \* Disorders of the pituitary gland or hypothalamus

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## GRAVE'S

(Hyperthyroidism)

- ~ A multisystem disorder consisting of a triad
  - \* Hyperthyroidism with diffuse hyperplasia of the thyroid gland
  - \* Infiltrative dermopathy
  - \* Infiltrative ophthalmopathy
- ~ Prevalence:
  - \* 20-40 year old female (F:M = 7:1)
  - \* Genetic link
- ~ Etiology:
  - \* Autoimmune disease: hypersensitivity reaction with thyroid stimulation by the circulation of abnormal thyroid-stimulating immunoglobulins (TSI)

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## Hashimoto's Thyroiditis

(Hypothyroidism)

- ~ The most common cause of hypothyroidism in the United States
- ~ It is named after the first doctor who described this condition, Dr. Hakaru Hashimoto, in 1912
- ~ Autoimmune disease
- ~ Goiter formation
- ~ 5-10 times more common in women than in men
- ~ The underlying cause of the autoimmune process still is unknown
  - \* Anti-TPO ab and Anti-TB recp ab present

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## Autoimmune atrophic thyroiditis

(Hypothyroidism)

- ~ Atrophic thyroiditis is similar to Hashimoto's thyroiditis
- ~ A goiter is not present

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## Postpartum Thyroiditis

(Hypothyroidism)

- ~ These women develop antibodies to their own thyroid during pregnancy, causing an inflammation of the thyroid after delivery

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## Systemic Manifestations of Hyperthyroid

(Primary or Secondary)

### ~ Symptoms

- \* Nervousness
- \* Heat intolerance
- \* Sweating
- \* Fatigue
- \* Palpitation
- \* Insomnia
- \* Early waking
- \* Alopecia
- \* Vitiligo
- \* Brittle nails

### ~ Signs

- \* Sweating
- \* Muscle Weakness
- \* Emotionally labile
- \* Tremor
- \* Tachycardia
- \* Arrhythmia
- \* Hypertension
- \* Brisk tendon reflex
- \* Diabetes
- \* ↑Triglycerides & Ca, ↓CHO
- \* Microcytic anemia
- \* Possible goiter
- \* Myxedema

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### Systemic Manifestations of Hypothyroidism (Primary or Secondary)

#### ~ Symptoms

- \* Cold intolerance
- \* Weakness
- \* Reduced energy
- \* Lethargy
- \* Muscle cramps
- \* Constipation
- \* Increased sleeping
- \* Weight gain
- \* Reduced appetite
- \* Joint stiffness

#### ~ Signs

- \* Cool, scaling skin
- \* Puffy hands and face
- \* Deep voice
- \* Myotonia
- \* Delirium
- \* Bradycardia
- \* Slow reflexes
- \* Obesity
- \* Hypothermia
- \* Myxedema

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### Thyroid Eye Disease (TED)

#### ~ Other names used

- \* Grave's disease
- \* Grave's ophthalmopathy
- \* Grave's orbitopathy
- \* Exophthalmos in Graves Disease
- \* Thyroid Associated Orbitopathy (TAO)
- \* Thyroid Orbitopathy
- \* Ophthalmic Graves Disease
- \* Inflammatory Eye Disease
- \* Endocrine Orbitopathy

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### Why is this so confusing?

#### ~ Thyroid Eye Disease

- \* Is often seen in conjunction with Graves' Disease (hyperthyroid)
- \* Is seen in people with no other evidence of thyroid dysfunction
- \* Is seen in patients who have Hashimoto's Disease (hypothyroid)

#### ~ Most thyroid patients, however, will not develop thyroid eye disease

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### Why is this so confusing?

#### ~ The eye symptoms usually occur at the same time as the thyroid disease

- \* However they may precede or follow the obvious symptoms of the thyroid abnormality

#### ~ The incidence of thyroid eye disease associated with thyroid dysfunction is higher and more severe in smokers

- \* There is no way to predict which thyroid patients will be affected

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### Why is this so confusing?

#### ~ While eye disease may be brought on by thyroid dysfunction

- \* Successful treatment of the thyroid gland does not guarantee that the eye disease will improve
- \* No particular thyroid treatment can guarantee that the eyes will not continue to deteriorate
- \* Once inflamed, the eye disease may remain active from several months to as long as three years
- \* There may be a gradual or, in some cases, a complete improvement

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### Thyroid Eye Disease

#### ~ Commonly known as Graves' ophthalmopathy

#### ~ About 80% of all patients with TED have the autoimmune hyperthyroid disorder known as Graves' disease

#### ~ Another 10% of all cases are seen in patients with autoimmune hypothyroidism, either Hashimoto's thyroiditis, atrophic thyroiditis or Hashitoxicosis

#### ~ Another 10% of all cases are seen in people with normal thyroid function

- \* When thyroid function is normal, the eye condition is referred to as euthyroid Graves' disease
- \* Euthyroid is a term meaning that thyroid function tests are normal. Most people with euthyroid Graves' disease develop a thyroid disorder within eighteen months of the emergence of the eye disorder
- \* But some people with euthyroid Graves' disease never develop thyroid dysfunction

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## Thyroid Eye Disease

~ What causes the Thyroid Eye Disease signs and symptoms?

- ~ The high and low levels of T3 and T4
- ~ The antibodies that are attacking the thyroid gland

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## Thyroid Eye Disease

~ Thyroid Eye Disease has 2 phases

- ★ A phase secondary to abnormal thyroid hormone levels
  - Increased or decreased FT3 and FT4 levels
  - Once these levels are normalized, ocular symptoms will resolve
- ★ Congestive Autoimmune form of Thyroid Eye Disease
  - Active phase-stimulating or blocking TRAb are causing ocular activity
  - Plateau phase-reduced activity
  - Resolution phase-symptoms regress and eyes return to normal

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### Phase secondary to abnormal thyroid hormone levels (T<sub>3</sub>/T<sub>4</sub>) (Thyroid Eye Disease)

~ Hyperthyroidism eye symptoms

- ★ Excess hormone acting on the nerves that supply the eye
- ★ Usually spastic and include staring
- ★ Dryness
- ★ Eyelid retraction

~ Hypothyroidism eye symptoms

- ★ Deficient hormone causing venous congestion, impaired circulation and fluid stagnation
- ★ Periorbital edema

- ~ This form of TED resolves within a few weeks after thyroid hormone levels (FT4 and FT3) are corrected and brought back into the normal range
- ~ The pituitary hormone TSH can stay low or suppressed for many months during the course of treatment for hyperthyroidism and doesn't mean that the patient is still hyperthyroid
- ~ TSH also lags at least 6 weeks behind thyroid hormone levels and often remains elevated longer in people who have been hypothyroid
- ~ Relying on the TSH level can be misleading and in treating TED

40

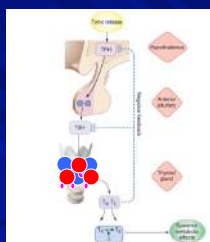
### Congestive Autoimmune form of Thyroid Eye Disease (Active phase, Plateau phase, Resolution phase)

- ~ Caused by both stimulating and blocking TSH receptor antibodies (TRAb) and also immune system chemicals known as cytokines
- ~ Secondary targets appear to be TSH receptor antigens (epitopes) located on orbital fibroblasts as well as dermal fibroblasts
- ~ Active "inflammatory" phase of TED varies
  - ★ Symptoms resolve quickly although on average the active phase lasts about 12-18 months
  - ★ TRAb levels are high, patients are smokers, nutrient deficiencies are present, or the patient continues to be exposed to environmental triggers such as excess dietary iodine, the active phase can last as long as 5 years
  - ★ Avoid any lid, muscle or orbital surgery
- ~ Plateau phase and Resolution "Passive" phase
  - ★ An individual may be left with structural changes, such as eye protrusion, eyelid retraction, and in some cases, double vision
  - ★ There are corrective procedures that can be performed to address these problems

41

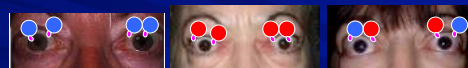
## Euthyroid Graves' disease

~ If thyroid function is normal.  
How does one develop thyroid eye disease?

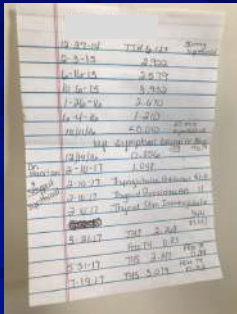


42

Similar receptors are found in the skin, fat and muscle of the orbit



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You're in the Know

Normal Values  
Thyroglobulin 20 IU/ml  
Peroxidase <35 IU/ml  
TSI 1.75 IU/ml

It does work!

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### General Ocular Symptoms

- ~ Prominent eyes, stare
- ~ Pain
- ~ Lacrimation
- ~ Eyelid swelling
- ~ Foreign-body sensation
- ~ Double vision
- ~ Photophobia
- ~ Decreased vision in one or both eyes

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### NOSPECS: Grading System

~ 1969 by S.C. Werner

- \* Class 0: No signs or symptoms
- \* Class 1: Only signs, upper lid retraction
- \* Class 2: Soft Tissue Involvement with symptoms
- \* Class 3: Proptosis
- \* Class 4: EOM Involvement
- \* Class 5: Corneal Involvement
- \* Class 6: Sight Loss

~ Class 2-6 document severity

- \* 0: absent
- \* A: minimal
- \* B: moderate
- \* C: marked

~ Within classes 2 to 6 the investigator has to differentiate the severity grades 0, A, B, C

~ NOSPECS, classifies severity but not the activity or stage (active/inflammatory or passive/congestive)

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### NOSPECS: Grading System

- ~ 0: No symptoms or signs
- ~ 1: Only signs (upper lid retraction without lid lag or proptosis)
- ~ 2: Soft tissue involvement with symptoms (excess lacrimation, sandy sensation, retrobulbar discomfort)
  - \* Grade 0: absent
  - \* Grade A: minimal (edema of lids, injection, sandy feeling)
  - \* Grade B: moderate (edema of lids, injection, chemosis, FBs, pain behind eyes)
  - \* Grade C: marked
- ~ 3: Proptosis associated with classes 2-6 only
  - \* Grade 0: absent
  - \* Grade A: minimal: 21mm -23mm
  - \* Grade B: moderate: 24mm -27mm
  - \* Grade C: marked: 28mm or more
  - \* Specify if inequality of ≥3 mm between eyes, or if progression of ≥3 mm under observation

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### NOSPECS: Grading System

- ~ 4: EOM involvement (usually with diplopia)
  - \* 0: absent
  - \* A: minimal (limitation of motion, patient reports diplopia but no obvious restriction)
  - \* B: moderate (evident restriction of motion)
  - \* C: marked (position of globe is fixed)
- ~ 5: Corneal involvement (due to proptosis, incomplete closure, lagophthalmos)
  - \* 0: absent
  - \* a: minimal (staining)
  - \* b: moderate (ulceration)
  - \* c: marked (clouding, necrosis, perforation)
- ~ 6: Sight loss (due to optic nerve involvement)
  - \* 0: absent
  - \* A: minimal (disc pallor or edema, or VF defect: vision 20/20-20/60)
  - \* B: moderate (same as A but VA 20/70-20/200)
  - \* C: marked (blindness, VA < 20/200)

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### LEMO Classification

- ~ 1991-Boergen and Pickardt
- ~ Complements NOSPECS
- ~ 4 finding-categories
  - \* Lid
  - \* Exophthalmos
  - \* Muscular
  - \* Optic nerve
- ~ Grade between 0 and 4 depending on severity
- ~ LEMO, classifies severity but not the activity or stage (active/inflammatory or passive/congestive)

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### LEMO Classification

#### Lid (L)

- 0: missing
- 1: lid edema only
- 2: real retraction (impaired lid closing)
- 3: retraction and upper lid edema
- 4: retraction and global lid edema

#### Exophthalmos (E)

- 0: missing
- 1: eye closing not impaired
- 2: conjunctival injection in the morning
- 3: persistent conjunctival injection
- 4: corneal complications

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### LEMO Classification

#### Muscular (M)

- 0: missing
- 1: detectable in imaging only
- 2: Pseudoparesis
- 3: Pseudoparalysis

#### Optic Nerve (O)

- 0: missing
- 1: regarding color vision only or detected via VEP
- 2: peripheral scotoma
- 3: central scotoma

LIEIM200  
Endocrine ophthalmopathy with lid edema, exophthalmos, pseudoparesis of external eye muscles, and no optic nerve involvement

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### Clinical Activity Score (CAS)

Thyroid disease characterized by:

- \* Severity
- \* Activity – want 3 or above
- CAS (1-7)

Studies for Tepezza

Payers using CAS for approval

- \* Due to wide open label
- \* Those infusing are charting the CAS

Table 3   Clinical Activity Score	
	Clinical Activity Score
1	Swelling behind globe
2	Pain on attempted gaze
3	Redness of eyelids
4	Redness of conjunctiva
5	Chemosis
6	Inflammatory eyelid swelling
7	Inflammation of conjunctival vessels
8	Increase of 2 mm in proptosis in last 3 months
9	Decrease in visual acuity in last 3 months
10	Decrease in eye movements of 10° in last 3 months

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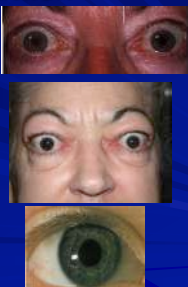
### Lid Involvement

- ~ Lid Retraction
- ~ Lid Lag
- ~ Lagophthalmus

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### Lid Retraction

- ~ Scleral show in primary gaze
- ~ Most commonly seen complication
- ~ Occurs in ~90% of Grave's patients
  - \* Excess stimulation of Muller's muscle
  - \* Fibrotic inferior rectus
  - \* Mechanical restriction or infiltration of levator
  - \* Increased orbital volume causes exophthalmos
- ~ Normal Lid Position
  - \* Upper lid intersects cornea at the 2 and 10 o'clock positions
    - ~2 mm below the limbus
  - \* Lower lid coincident or 1-2mm below the limbus



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### Eyelid Lag: von Graefe's Sign

- ~ Immobility or lagging of upper eyelid on downward gaze
- ~ Fibrosis of the inferior rectus muscle may induce lower lid retraction



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## Lagophthalmos

- ~ Inability to form a complete lid closure with a normal blink due to Exophthalmos/ Proptosis
- ~ Often leads to corneal exposure

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## Soft Tissue Involvement

- ~ Conjunctiva
- ~ Chemosis
- ~ Periorbital edema

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## Conjunctiva

- ~ Conjunctival and episcleral injection
  - \* Especially near the horizontal recti insertions
- ~ Chemosis
  - \* Edema of the conjunctiva and caruncle
- ~ Superior Limbic Keratoconjunctivitis
  - \* 65% correlation between SLK and systemic thyroid disease
  - \* Rheumatoid arthritis
  - \* Sjögren's syndrome



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"If it is Red think TED"

Dr. Andy Morgenstern 12-7-2013, OMS-Contemporary Resort



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## Periorbital Edema

- ~ Inflammation of the subcutaneous connective tissue
- ~ May be first sign of thyroid eye disease
- ~ Greatest in the morning



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## Infiltrative Orbitopathy (Exophthalmos/Proptosis)

- ~ Thyroid Eye Disease is most common cause of unilateral and bilateral exophthalmos
- ~ The term exophthalmos is reserved for prominence of the eye secondary to thyroid disease
- ~ May need MRI to determine or obvious exophthalmos may be present
- ~ It is permanent in 70% of cases
- ~ Caused by increased volume of the extra ocular muscles
  - \* Lymphocytic infiltration
  - \* Proliferation of fibroblasts
  - \* Edema within the interstitial tissue of the muscle

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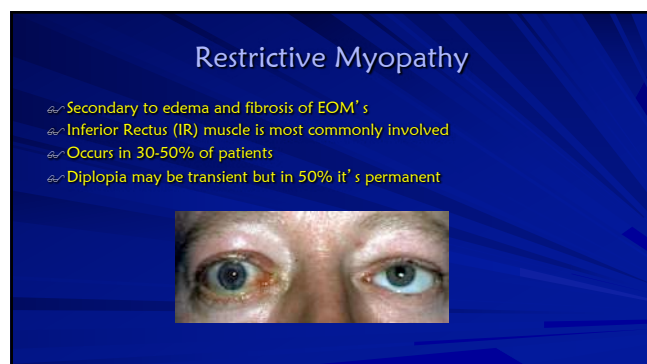
64

**Exophthalmometry**

- Is race dependent (Asians versus Black men is statistically significant)
- Hertel or Luedde results
- Adults
  - Average reading 17 mm
  - 95% of population have readings between 13-21mm
- General concerns
  - A difference of 2 mm or more between the eyes
  - A measurement of more than 24 mm

Race	Mean Normal Value	Upper Limits
	mm	mm
White women	15.4	20.1
White men	16.5	21.7
Black women	17.8	23.1
Black men	18.5	24.7
Asians	----	18.0

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**IOP in Thyroid Eye Disease**

- A rise in IOP has been reported with TED
- I would have higher suspicion when you see
  - Periorbital edema
  - Exophthalmos, proptosis
  - Restrictive myopathy
- Some literature reports IOP in up gaze to be part of the diagnoses of thyroid dysfunction

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### Restrictive Myopathy

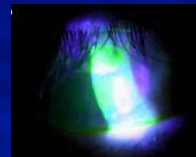


Obvious restrictive myopathy but also note the periorbital edema, and conjunctival hyperemia

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### Corneal Exposure

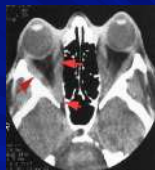
- Exposure keratopathy secondary to exophthalmos and lagophthalmos
- Significant threat to visual function



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### Optic Neuropathy

- Affects 5% of patients
- Usually mild to moderate exophthalmos and shallow orbits
- Enlargement of the recti muscles compresses ONH or its blood supply at the apex of the orbit
- Compression MAY occur without significant proptosis
- Compressive and/or ischemic and/or toxic



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### Treatment of Thyroid Eye Disease

- Depends on what phase of the disease we are in:
  - Phase secondary to abnormal thyroid hormone levels
  - Active "inflammatory" phase
  - Plateau phase and Resolution "Passive" phase
- Depends on what orbital tissue or structures are involved
- Depends on the risk of vision loss
- Depends if primary, secondary or tertiary thyroid dysfunction
- Management consists of:
  - Control of inflammation
  - Prevention of ocular and visual damage
  - Addressing ocular motor abnormalities
  - Improving cosmetic disfigurement
- Patient education is essential
- Communication with an endocrinologist or internist will ensure proper patient care

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### Treatment of Thyroid Eye Disease

- Palliative (hormone imbalance, active, passive)
  - Lubricants
  - Topical anti-inflammatory (Lotemax/Restasis)
  - Prisms
- Steroids (active phase)
  - Orals
  - Peri-ocular injections
  - IV with oral steroid taper
- Orbital radiotherapy (active phase)
- Orbital Decompression (passive phase)
  - Fat removal orbital decompression (FROD)
    - Large orbits
  - Bone removal orbital decompression (BROD)
    - Small orbits
  - Both FROD and BROD



Smoking causes the thyroid eye disease to be more severe  
Smoking causes treatments to be less effective

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### Treatment of Thyroid Eye Disease

- Paradigm shifts
  - Decrease in orbital radiotherapy
  - Waiting for passive stage but doing surgery
  - Increase usage of fat removal orbital decompression as first approach
  - Peri-orbital injection of steroids for recurrent disease after orals
- Future
  - Looking for better or different ways to treat the active phase of this disease

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### Lid Retraction, Eyelid Lag, Lagophthalmos

- Must treat underlying thyroid dysfunction
- Abnormal hormone level and Active phase
  - \* Treat the exposure keratitis with lubricants
  - \* Tape eyelids shut at night
  - \* Lid weight
  - \* Moisture chamber at night
  - \* Antibiotic ointments
- Passive Phase
  - \* Surgical Management
  - \* Inferior rectus recession
  - \* Mullerotomy
  - \* Recession of lower lid retractors



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### Lid Retractor Surgery



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### Conjunctiva, Periorbital edema

- Topical lubricants
  - \* Artificial tears
  - \* Ointments at night
  - \* Topical steroids
  - \* Restasis?
- Tape eyelids closed at night or use mask
- Elevate head at night to decrease lid edema
- Oral diuretics Acetazolamide
- Oral steroids
  - \* 60-80mg/day for 3 months
- IV steroids
- Periorbital steroids
  - \* Kenalog last 1 month



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### Infiltrative Orbitopathy (Exophthalmos/Proptosis)

- Orbital Disease Consult
  - \* Systemic steroids to reduce inflammation
  - \* Low dose radiotherapy
  - \* Surgical orbital decompression



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### Restrictive Myopathy

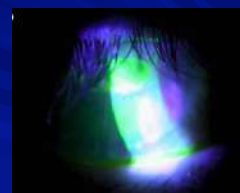
- Non-surgical (while waiting for stability)
  - \* Teach proper head position to alleviate diplopia
  - \* Prism in spectacle correction (Fresnel or ground in)
  - \* Oral steroids
  - \* Botulinum toxin injection
- Surgical Consult
  - \* Recession of the rectus muscle/s involved
  - \* Diplopia in primary gaze, reading gaze or both
  - \* Stable angle of deviation for at least 6 months
  - \* No evidence of active disease
  - \* Binocular vision in at least primary and reading positions



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### Corneal Exposure

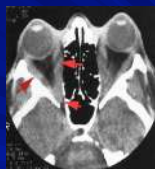
- Manage the corneal defect as first line
  - \* Lubricating and antibiotic
  - \* Lid taping
  - \* Moisture barrier
- Orbital Disease Consult
  - \* High dose oral steroids
    - 120-140mg /day x 7 days
  - \* Orbital decompression



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## Optic Neuropathy

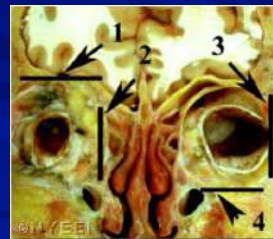
- ~ Systemic Steroids
  - \* If rapidly progressive and painful in the early stage of the disease
  - \* Only if no contraindications
  - \* Prednisolone 80-100mg, expect results within 48hrs. Taper dose and d/c within 3 mo
- ~ IV Methylprednisolone
- ~ Radiotherapy; if contraindication to steroid
- ~ Orbital decompression



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## Orbital Decompression

- ~ Not effective if no medical treatment
  - \* Two-wall decompression
    - 3-6 mm retro-placement of the globe
  - \* Three-wall decompression
    - 6-10mm retro-placement
  - \* Four-wall decompression
    - 10-16mm retro-placement



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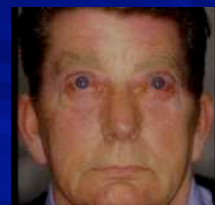
## Orbital Decompression (Surgical/Cosmetic)



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## Thyroid Eye Disease and Depression

- ~ When facial disfigurement occurs, thyroid eye disease is equivalent to the diagnosis of cancer and AIDS



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## Orbital Decompression (Medical/Vision Threatened)

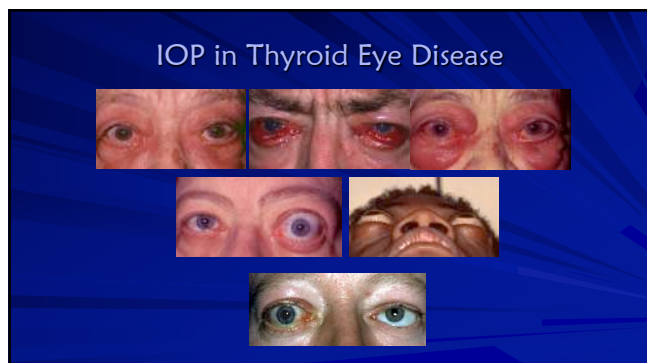


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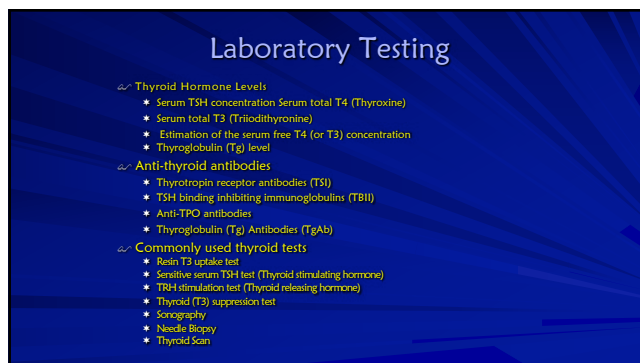
## IOP in Thyroid Eye Disease

- ~ A rise in IOP has been reported with TED
- ~ I would have higher suspicion when you see
  - \* Periorbital edema
  - \* Exophthalmos, proptosis
  - \* Restrictive myopathy
- ~ Some literature reports IOP in up gaze to be part of the diagnoses of thyroid dysfunction....let's discuss

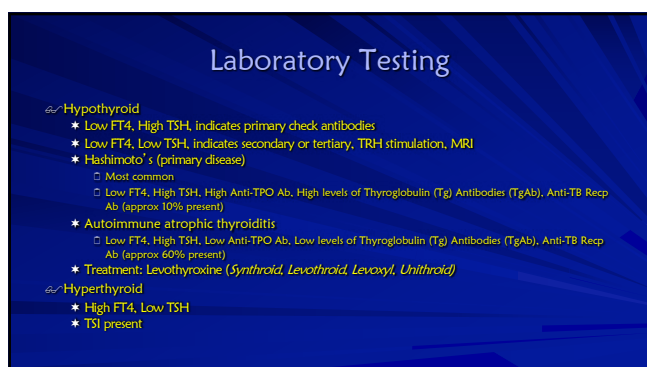
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86



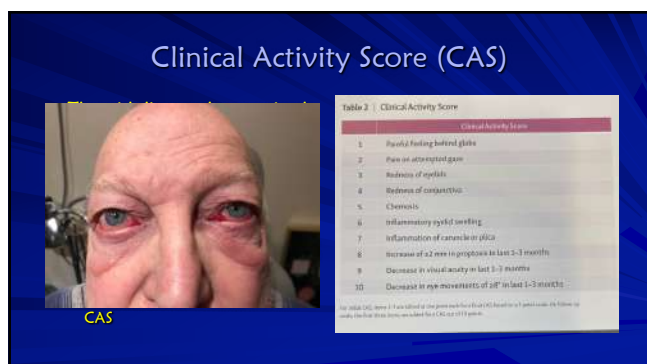
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April 22, 2019



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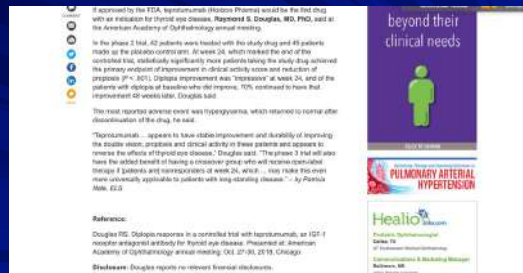
April 22, 2019



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100



101

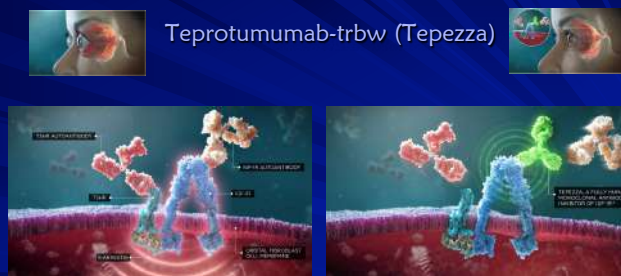
## Teprotumumab-trbw (Tepezza)

- Horizon Therapeutics – HQ Dublin, Ireland and US based Chicago
- Biologic pharmaceutical
  - Chinese Hamster Ovary
  - Infusion, 8 total, every 3 weeks
- Thyroid eye disease
  - IGF-1 (Insulin like growth factor I) and TSH receptors are over expressed
  - IGF-1 receptor inhibitor monoclonal antibody
    - On the orbital fibroblasts
      - Inhibiting downstream inflammatory cascade
        - Cytokines, hyaluron, leukotriene
        - Differentiation into adipocytes and myofibroblasts
- Phase 2 and published in New England Journal of Medicine
- Phase 3 completed
  - Published - New England Journal of Medicine
- PDUFA: March 2020, was approved early in 2020



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## Teprotumumab-trbw (Tepezza)



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## Immunosuppression?

- ~ **Biologics**
  - ★ Immunosuppression biologics – suppress the immune system to get the effect
  - Remicade – “1st generation”
    - Chimeric molecule – mouse and human protein, a lot of sensitivity
  - Humira
    - Anti-TNF (RA and Crohn’s Disease)
    - Fully human protein, less sensitivity
  - Rituxan
    - CD 20 suppressor (B cell suppression)
  - Actively suppress the immune system
- ★ Immunomodulatory
  - Tepezza
    - IGF-1R inhibitor
    - Full humanized monoclonal antibody
      - All the proteins are human – less to no sensitivity – more focused effect
    - Orbital fibroblasts to myofibroblast or adipocytes
    - Hyaluronic acid, glycosaminoglycan

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## Teprotumumab-trbw (Tepezza)

- ~ **Optics and Optic-X Studies**
  - ★ 8 infusions, every 3 weeks, 24 weeks
  - ★ Optics – acute, less than 9 months of disease
  - ★ Optics X – chronic, 12-16 months disease
- ~ **Clinical Activity Score**
  - ★ Spontaneous pain, gaze evoked pain, eyelid erythema, chemosis, inflammation
  - ★ Scale of 7, needed 4 to be in the study
- ~ **Proptosis**
  - ★ Improvement of 2 mm or better
- ~ **Diplopia**
  - ★ Scale of 0, 1, 2, or 3
- ~ **Grave’s Ophthalmopathy -Quality of Life Score**
  - ★ Scale 0-100

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## Teprotumumab-trbw (Tepezza)

- ~ **Clinical Activity Score (CAS)**
  - ★ Spontaneous pain, gaze evoked pain, eyelid erythema, chemosis, inflammation
  - ★ Scale of 7, needed 4 to be in the study
    - 78% improved to 0 or 1, 7% improved 0 or 1 with placebo
- ~ **Proptosis**
  - ★ Improvement of 2 mm or better
    - 83% had 2 mm or better, 10% with placebo
    - Average was 3.2 mm at week 24
- ~ **Diplopia**
  - ★ Scale of 0, 1, 2, or 3
    - 68% improved 1 point, 29% with placebo
- ~ **Grave’s Ophthalmopathy -Quality of Life Score**
  - ★ Scale 0-100
    - 17.28 point improved, 1.80 with placebo

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## Teprotumumab-trbw (Tepezza)

- ~ **Adverse Reactions**
  - ★ **Very well tolerated**
  - ★ The most common adverse reactions (incidence ≥5% and greater than placebo) are muscle spasm, nausea, alopecia, diarrhea, fatigue, hyperglycemia, hearing impairment, dysgeusia, headache, and dry skin.

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## Teprotumumab-trbw (Tepezza)

- ~ **Infusion Reactions (mild/moderate):** approximately 4% of patients
  - ★ transient increases in blood pressure, feeling hot, tachycardia, dyspnea, headache, and muscular pain
  - ★ consideration should be given to premedicating with an antihistamine, antipyretic, or corticosteroid and/or administering at a slower infusion rate.
- ~ **Hyperglycemia:** Increased blood glucose or hyperglycemia
  - ★ In clinical trials, 10% of patients experienced hyperglycemia
  - ★ Monitor patients for elevated blood glucose and symptoms of hyperglycemia while on treatment with teprotumumab
  - ★ Patients with preexisting diabetes should be euglycemic before beginning treatment

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## Teprotumumab-trbw (Tepezza)

- ~ **Infusion center**
  - ★ Go to Horizon website
  - ★ Contact Us
  - ★ Type in your question
    - Looking for infusion center

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## Biologics Used Off Label for TED

Table 1 | Biologic therapies for TED

Small Molecule Therapy	Target	Dosing	Results	Side Effects
Humira®	CD20	2 infusions of 500 mg each, 2 weeks apart	Most results in improvement of OGD, ptosis, and exophthalmos	Local infection, lymphoma, hepatitis
Abatacept®	TNF-α	Subcutaneous injections of 100 mg every 2 weeks for 18 weeks	Most studies show improvement in inflammation, but no change in ptosis or exophthalmos	Upper OGD
Infliximab	TNF-α	Infusions at 5 mg/kg each dose over 2 years	Case reports showed improvement in inflammation, OGD, and exophthalmos	Infection, malignancy, hepatitis, lymphoma, drug-induced liver
Tacrolimus	IL-2	3 infusions at 0.1 mg/kg every 4 weeks	STX with tacrolimus improved OGD, most studies showed improvement in OGD	High incidence of side effects, particularly
Trastuzumab	HER-2	Initial infusion of 12 mg/kg, followed by 2 infusions at 6 mg/kg every 3 weeks	Most studies show improvement in OGD, exophthalmos, and ptosis, but some studies show no change in OGD	Most common: acute myeloid leukemia, lymphoma, leukemia, liver failure, heart failure, and other

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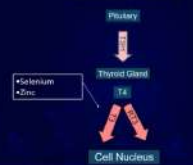
## Key Tenants of Aging, Performance and Vitality

- Oxidative Stress / Inflammation
- Hormonal Balance
- Stress Hormones
- Glucose / Insulin Regulation
- GUT integrity and microbiome diversity
- Immune Balance
- Environmental Exposure/Burden
- Individuality

Credit to: James LaVelle, RPh, CCN

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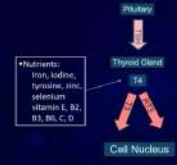
## Thyroid Function: Factors increasing conversion of T4 to T3



Credit to: Filomena Trindade, MD

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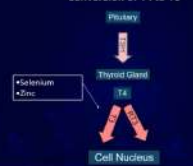
## What Effects Thyroid Function: Production of Thyroid Hormones



Credit to: Filomena Trindade, MD

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## Thyroid Function: Factors increasing conversion of T4 to T3



Credit to: Filomena Trindade, MD

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## Thyroid Hormones: Factors improving cellular sensitivity to thyroid hormones



Credit to: Filomena Trindade, MD

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**Thyroid Function: Inhibitors of Thyroid Hormone Production:**

- Pituitary:**
  - Stress
  - Infection, trauma, radiation, medications
  - Primary hypopituitarism to hypothalamus
  - Thyroid peroxidase, heavy metals, autoimmune disease, pituitary
  - Autoimmune disease, iodine deficiency
  - Concurrent, recovery or lead toxicity
- Thyroid Gland:**
  - Stress
  - Low iodine intake
  - High iodine dose
  - Decreased cofactor
  - Thyroiditis
  - Decreased iodine or liver function

Credit to: Filomena Trindade, MD

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**Thyroid Function: Factors Decreasing conversion of T4 to T3**

- Pituitary:**
  - Stress
  - Trauma
  - Low-iodine diet
  - Inflammation (cytokines, etc.)
- Thyroid Gland:**
  - Toxins
  - Infections
  - Liver/kidney dysfunction
  - Rx medications

Credit to: Filomena Trindade, MD

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**Two Major Pathways of Metabolism & Detoxification**

Phase I: Reactive Intermediate → Phase II: Elimination

Influencing factors: Gut Flora, Oxidative Stress, Nutrients (Vitamin A, Vitamin E, Vitamin C, Vitamin B, Vitamin D, Vitamin K, Vitamin F, Vitamin G, Vitamin H, Vitamin I, Vitamin J, Vitamin K, Vitamin L, Vitamin M, Vitamin N, Vitamin O, Vitamin P, Vitamin Q, Vitamin R, Vitamin S, Vitamin T, Vitamin U, Vitamin V, Vitamin W, Vitamin X, Vitamin Y, Vitamin Z, Vitamin AA, Vitamin AB, Vitamin AC, Vitamin AD, Vitamin AE, Vitamin AF, Vitamin AG, Vitamin AH, Vitamin AI, Vitamin AJ, Vitamin AK, Vitamin AL, Vitamin AM, Vitamin AN, Vitamin AO, Vitamin AP, Vitamin AQ, Vitamin AR, Vitamin AS, Vitamin AT, Vitamin AU, Vitamin AV, Vitamin AW, Vitamin AX, Vitamin AY, Vitamin AZ, Vitamin BA, Vitamin BB, Vitamin BC, Vitamin BD, Vitamin BE, Vitamin BF, Vitamin BG, Vitamin BH, Vitamin BI, Vitamin BJ, Vitamin BK, Vitamin BL, Vitamin BM, Vitamin BN, Vitamin BO, Vitamin BP, Vitamin BQ, Vitamin BR, Vitamin BS, Vitamin BT, Vitamin BU, Vitamin BV, Vitamin BW, Vitamin BX, Vitamin BY, Vitamin BZ, Vitamin CA, Vitamin CB, Vitamin CC, Vitamin CD, Vitamin CE, Vitamin CF, Vitamin CG, Vitamin CH, Vitamin CI, Vitamin CJ, Vitamin CK, Vitamin CL, Vitamin CM, Vitamin CN, Vitamin CO, Vitamin CP, Vitamin CQ, Vitamin CR, Vitamin CS, Vitamin CT, Vitamin CU, Vitamin CV, Vitamin CW, Vitamin CX, Vitamin CY, Vitamin CZ, Vitamin DA, Vitamin DB, Vitamin DC, Vitamin DD, Vitamin DE, Vitamin DF, Vitamin DG, Vitamin DH, Vitamin DI, Vitamin DJ, Vitamin DK, Vitamin DL, Vitamin DM, Vitamin DN, Vitamin DO, Vitamin DP, Vitamin DQ, Vitamin DR, Vitamin DS, Vitamin DT, Vitamin DU, Vitamin DV, Vitamin DW, Vitamin DX, Vitamin DY, Vitamin DZ, Vitamin EA, Vitamin EB, Vitamin EC, Vitamin ED, Vitamin EE, Vitamin EF, Vitamin EG, Vitamin EH, Vitamin EI, Vitamin EJ, Vitamin EK, Vitamin EL, Vitamin EM, Vitamin EN, Vitamin EO, Vitamin EP, Vitamin EQ, Vitamin ER, Vitamin ES, Vitamin ET, Vitamin EU, Vitamin EV, Vitamin EW, Vitamin EX, Vitamin EY, Vitamin EZ, Vitamin FA, Vitamin FB, Vitamin FC, Vitamin FD, Vitamin FE, Vitamin FF, 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Credit to: Filomena Trindade, MD

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**The Relationship between Gastrointestinal Health, Micronutrient Concentrations, and Autoimmunity: A Focus on the Thyroid**

Abstract: Currently, there is a lack of understanding of why many patients with thyroid dysfunction (hyperthyroidism, hypothyroidism, autoimmune thyroiditis, Hashimoto's thyroiditis) have associated autoimmune diseases, such as celiac disease, type 1 diabetes mellitus, and autoimmune gastritis. The autoimmune reaction may be related to the impact of the gut microbiome on the immune system. The impact of the gut microbiome on the immune system is a complex process involving many factors, including the gut barrier, the gut immune system, and the gut-brain axis. This review aims to provide an overview of the current knowledge on the relationship between gastrointestinal health, micronutrient concentrations, and autoimmunity, with a focus on the thyroid.

Credit to: Filomena Trindade, MD

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**Key Thyroid Nutrients**

Gut Flora → Key Thyroid Nutrients → Gut Treatments Improve Thyroid Health

Credit to: Filomena Trindade, MD

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**Skin Carotenoid Levels**

Oxidative Stress/Inflammation/Anti-Oxidant Deficient

NIH National Institutes of Health

Quick Test (approx. 30 sec)

Portable

Cost Effective

Remeasure in 60 days

Reassurance to you and patient

Credit to: Filomena Trindade, MD

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Ingredients		
Ingredients	Amount	% Daily Value
<b>Serving Size: 1 Packet</b>		
Vitamin A (as Beta Carotene 100% RAE from Marigold extract and Vitamin A palmitate 25% RAE)	2750 mcg RAE	250%
Vitamin C (as Ascorbic Acid)	2100 mg	210%
Vitamin E (as D-Alpha Tocopherol Acetate, D-Alpha Tocopherol, Tocotrienols)	100 mg	100%
Vitamin K (as Phytylphosphatide)	100 mcg	100%
Vitamin B1 (as Thiamine Mononitrate)	25 mg	250%
Vitamin B2 (as Riboflavin)	25 mg	250%
Vitamin B3 (as Nicotinamide)	100 mg	100%
Vitamin B5 (as Pantoic Acid)	100 mg	100%
Vitamin B6 (as Pyridoxine Hydrochloride)	100 mg	100%
Vitamin B12 (as Cyanocobalamin)	100 mcg	100%
Vitamin D3 (as Cholecalciferol)	100 mcg	100%
Vitamin D4 (as Calciferol)	100 mcg	100%
Vitamin D5 (as Calciferol)	100 mcg	100%
Vitamin D6 (as Calciferol)	100 mcg	100%
Vitamin D7 (as Calciferol)	100 mcg	100%
Vitamin D8 (as Calciferol)	100 mcg	100%
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Vitamin D90 (as Calciferol)	100 mcg	100%
Vitamin D91 (as Calciferol)	100 mcg	100%
Vitamin D92 (as Calciferol)	100 mcg	100%
Vitamin D93 (as Calciferol)	100 mcg	100%
Vitamin D94 (as Calciferol)	100 mcg	100%
Vitamin D95 (as Calciferol)	100 mcg	100%
Vitamin D96 (as Calciferol)	100 mcg	100%
Vitamin D97 (as Calciferol)	100 mcg	100%
Vitamin D98 (as Calciferol)	100 mcg	100%
Vitamin D99 (as Calciferol)	100 mcg	100%
Vitamin D100 (as Calciferol)	100 mcg	100%

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Supplement Facts		
Supplement Facts	Amount	% Daily Value
Vitamin A (as Beta Carotene 100% RAE from Marigold extract and Vitamin A palmitate 25% RAE)	2750 mcg RAE	250%
Vitamin C (as Ascorbic Acid)	2100 mg	210%
Vitamin E (as D-Alpha Tocopherol Acetate, D-Alpha Tocopherol, Tocotrienols)	100 mg	100%
Vitamin K (as Phytylphosphatide)	100 mcg	100%
Vitamin B1 (as Thiamine Mononitrate)	25 mg	250%
Vitamin B2 (as Riboflavin)	25 mg	250%
Vitamin B3 (as Nicotinamide)	100 mg	100%
Vitamin B5 (as Pantoic Acid)	100 mg	100%
Vitamin B6 (as Pyridoxine Hydrochloride)	100 mg	100%
Vitamin B12 (as Cyanocobalamin)	100 mcg	100%
Vitamin D3 (as Cholecalciferol)	100 mcg	100%
Vitamin D4 (as Calciferol)	100 mcg	100%
Vitamin D5 (as Calciferol)	100 mcg	100%
Vitamin D6 (as Calciferol)	100 mcg	100%
Vitamin D7 (as Calciferol)	100 mcg	100%
Vitamin D8 (as Calciferol)	100 mcg	100%
Vitamin D9 (as Calciferol)	100 mcg	100%
Vitamin D10 (as Calciferol)	100 mcg	100%
Vitamin D11 (as Calciferol)	100 mcg	100%
Vitamin D12 (as Calciferol)	100 mcg	100%
Vitamin D13 (as Calciferol)	100 mcg	100%
Vitamin D14 (as Calciferol)	100 mcg	100%
Vitamin D15 (as Calciferol)	100 mcg	100%
Vitamin D16 (as Calciferol)	100 mcg	100%
Vitamin D17 (as Calciferol)	100 mcg	100%
Vitamin D18 (as Calciferol)	100 mcg	100%
Vitamin D19 (as Calciferol)	100 mcg	100%
Vitamin D20 (as Calciferol)	100 mcg	100%
Vitamin D21 (as Calciferol)	100 mcg	100%
Vitamin D22 (as Calciferol)	100 mcg	100%
Vitamin D23 (as Calciferol)	100 mcg	100%
Vitamin D24 (as Calciferol)	100 mcg	100%
Vitamin D25 (as Calciferol)	100 mcg	100%
Vitamin D26 (as Calciferol)	100 mcg	100%
Vitamin D27 (as Calciferol)	100 mcg	100%
Vitamin D28 (as Calciferol)	100 mcg	100%
Vitamin D29 (as Calciferol)	100 mcg	100%
Vitamin D30 (as Calciferol)	100 mcg	100%
Vitamin D31 (as Calciferol)	100 mcg	100%
Vitamin D32 (as Calciferol)	100 mcg	100%
Vitamin D33 (as Calciferol)	100 mcg	100%
Vitamin D34 (as Calciferol)	100 mcg	100%
Vitamin D35 (as Calciferol)	100 mcg	100%
Vitamin D36 (as Calciferol)	100 mcg	100%
Vitamin D37 (as Calciferol)	100 mcg	100%
Vitamin D38 (as Calciferol)	100 mcg	100%
Vitamin D39 (as Calciferol)	100 mcg	100%
Vitamin D40 (as Calciferol)	100 mcg	100%
Vitamin D41 (as Calciferol)	100 mcg	100%
Vitamin D42 (as Calciferol)	100 mcg	100%
Vitamin D43 (as Calciferol)	100 mcg	100%
Vitamin D44 (as Calciferol)	100 mcg	100%
Vitamin D45 (as Calciferol)	100 mcg	100%
Vitamin D46 (as Calciferol)	100 mcg	100%
Vitamin D47 (as Calciferol)	100 mcg	100%
Vitamin D48 (as Calciferol)	100 mcg	100%
Vitamin D49 (as Calciferol)	100 mcg	100%
Vitamin D50 (as Calciferol)	100 mcg	100%
Vitamin D51 (as Calciferol)	100 mcg	100%
Vitamin D52 (as Calciferol)	100 mcg	100%
Vitamin D53 (as Calciferol)	100 mcg	100%
Vitamin D54 (as Calciferol)	100 mcg	100%
Vitamin D55 (as Calciferol)	100 mcg	100%
Vitamin D56 (as Calciferol)	100 mcg	100%
Vitamin D57 (as Calciferol)	100 mcg	100%
Vitamin D58 (as Calciferol)	100 mcg	100%
Vitamin D59 (as Calciferol)	100 mcg	100%
Vitamin D60 (as Calciferol)	100 mcg	100%
Vitamin D61 (as Calciferol)	100 mcg	100%
Vitamin D62 (as Calciferol)	100 mcg	100%
Vitamin D63 (as Calciferol)	100 mcg	100%
Vitamin D64 (as Calciferol)	100 mcg	100%
Vitamin D65 (as Calciferol)	100 mcg	100%
Vitamin D66 (as Calciferol)	100 mcg	100%
Vitamin D67 (as Calciferol)	100 mcg	100%
Vitamin D68 (as Calciferol)	100 mcg	100%
Vitamin D69 (as Calciferol)	100 mcg	100%
Vitamin D70 (as Calciferol)	100 mcg	100%
Vitamin D71 (as Calciferol)	100 mcg	100%
Vitamin D72 (as Calciferol)	100 mcg	100%
Vitamin D73 (as Calciferol)	100 mcg	100%
Vitamin D74 (as Calciferol)	100 mcg	100%
Vitamin D75 (as Calciferol)	100 mcg	100%
Vitamin D76 (as Calciferol)	100 mcg	100%
Vitamin D77 (as Calciferol)	100 mcg	100%
Vitamin D78 (as Calciferol)	100 mcg	100%
Vitamin D79 (as Calciferol)	100 mcg	100%
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Vitamin D85 (as Calciferol)	100 mcg	100%
Vitamin D86 (as Calciferol)	100 mcg	100%
Vitamin D87 (as Calciferol)	100 mcg	100%
Vitamin D88 (as Calciferol)	100 mcg	100%
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### Key Tenants of Aging, Performance and Vitality

- Oxidative Stress / Inflammation
- Hormonal Balance
- Stress Hormones
- Glucose / Insulin Regulation
- GUT integrity and microbiome diversity
- Immune Balance
- Environmental Exposure/Burden
- Individuality


Credit to: James LaValle, RPh, CCM

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### Signs in Thyroid Eye Disease

- Dalrymple's sign: Lid retraction
- von Graefe's sign: Upper lid lag on downward gaze
- Griffith's sign: Lower lid lag on downward gaze
- Boston's sign: Jerky irregular movement of the upper lid on downward gaze
- Jellinek's sign: Increased pigmentation of the lids
- Stellwag's sign: Infrequent blinking
- Kocher's sign: Increased lid retraction with visual fixation
- Enroth's sign: Puffy swelling of the lids
- Rosenbach's sign: Tremor of closed lids
- Mobius' sign: Weakness of convergence
- Ballet's sign: Palsy of one or more extraocular muscles
- Suker's sign: Weakness of fixation on lateral gaze
- Cowen's sign: Jerky papillary contraction to consensual light
- Kries' sign: Unequal dilatation of the pupils
- Jeffrey's sign: Absence of forehead wrinkling on upward gaze


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### Questions and Thank You!

#### Thyroid and Thyroid Eye Disease Clinical Pearls and Innovations for 2023

Greg Caldwell, OD, FAOA  
Pittsburgh Primary Eye Care Conference  
Saturday, February 18, 2023



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