THYROID DISEASE AND THE EYE: WHAT WE MUST KNOW

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Disclosures: My lectures and research have been supported by the following:

- Alcon
- Allergan
- TearLab
- Valeant (Lacrisert)
- Odyssey Medical
- Johnson & Johnson Vision
- Science Based Health
- Shire
- NovaBay
- Wineries
Why?

- …do women account for the vast majority of patients w/ thyroid disease?
- …do people who have hyperthyroid disease develop dry eye?
- …do people who have hypothyroid disease develop dry eye?
- …do patients with hyperthyroidism typically convert to hypothyroid disease?
Endocrine System: Basic Science
Organisms are constantly exposed to change
Capacity to respond to change is inherent to living things

Maintenance of homeostasis is vital to well-being & survival, but it requires communication
Implications for Communication: Simple to Complex

- One celled organisms - minimal communication
- Simple organisms - limited communication
- Complex organisms - sophisticated communication
Communication and Homeostasis

- When situations require a focal, rapid response
  - Speed is critical
  - Utilization of resources - minimal importance
  - Hard wired “point-to-point”
  - Impulses travel along nerves
- When situations demand widespread reaction
  - Speed may not be critical
  - Reaching multiple target tissues is crucial
  - Resources need to be conserved
  - Potential to reach every cell

Nervous System

Endocrine System
Endocrine Regulation is Vital

- Growth
- Development
- Metabolism
- Electrolyte balances
- Reproduction

Central Control Centers

- Hypothalamus – region not gland
  - Releasing & inhibiting hormones
- Pituitary gland- endocrine gland
  - Hormones reach circulation, act on:
Hormonal Receptor Selectivity

- A hormone only affects a target cell when hormone-specific receptors are on the cell membrane.
- Cells lacking receptors to a specific hormone will not react to it, regardless of concentration.

Hormonal selectivity is crucial to proper functioning of the endocrine system.
Thyroid Gland

- Butterfly-shaped gland overlying larynx
  - Overlies recurrent laryngeal nerve
- Iodine
  - Thyroid gland contains 30% of body’s iodine
  - Essential to thyroid hormone synthesis*
- Functional structure- follicles
  - Absorb iodine from circulation
  - Synthesize thyroid hormones
- Hormone synthesis- colloid
  - Release hormones \( \Rightarrow \) circulation
  - Strongly influence tissues, functions
Thyroid produces two hormones:

- Thyroxine (T4) 90% - 4 iodine molecules
- Triiodothyronine (T3) 10% - 3 iodine molecules

- T3 more biologically powerful & acts more rapidly
- Liver & kidneys convert a portion of circulating T4
Effects of Thyroid Hormones

- INCREASE
  - Heart rate
  - Cardiac contractility
  - Cardiac output
  - Alertness

- STIMULATE
  - Carbohydrate metabolism
  - Protein synthesis
  - Fat mobilization
  - Plasma concentrations of fatty acids

Thyroid hormones are very powerful molecules!
THE POWER OF HORMONES MUST BE CLOSELY CONTROLLED

- Receptors detect low hormone levels & stimulates production
- Adequate or excessive hormone levels trigger negative feedback loop
- Feedback system prevents effects of excessive or deficient hormones levels
- Failure to regulate hormone release results in hyper-abundance of hormones
Risk Factors for Thyroid Disorders

- Gender: females
  - 13% lifetime risk (1 in 8) for developing a thyroid disorder
  - Five to eight times greater risk than males
- Age:
  - Individuals over 50 have a higher risk of thyroid disease
  - Males’ risk for thyroid disease increases after age 60
- Radiation exposure- thyroid highly susceptible to radiation
  - Increases risk of thyroid disease
  - Highest risk head and neck region, childhood
- Diet: deficiency or absence of dietary iodine

Overall prevalence: 1 in 13 persons (7.35% or 22M)
Undiagnosed prevalence in USA: 1 in 20 or 13 M
Thyroid-associated Disorders

- Hypothyroidism
- Hyperthyroidism
- Thyroid cancer
- Thyroid nodules
- Thyroid associated eye disease (TAED)
- Euthyroid Grave’s Disease
What other autoimmune condition does this patient have?
Hypothyroidism

#2 endocrine disorder in US: 1° Hashimoto’s
Reduced or no production of thyroid hormones

Findings Associated w/ hypothyroidism

Weight increase @ onset of disease
- Females 64.5 (131 lb) to 70.2 kg (141 lb) 10 lb gain
- Males 82.8 (167 lb) to 85.6 kg (172 lb) 5 lb gain

Goiter- enlarged thyroid gland
When Thyroid Hormone Levels Fall, Body Functions Decline

- Reduced overall metabolic rate
- Slower heart rate (bradycardia)
- Reduced body temperature
- Mood, alertness (lethargy, reduced mentation)
- Reduced protein production
- Skin, hair changes
- Lipid metabolism (elevated LDL)
- Females w hypothyroid = 2x risk for cardiac
Iodine deficiency disorders – rare in USA today

- Before the 1920s, common in the Great Lakes, Appalachians, Northwest, and Canada– soil iodine
- Endemic goiter- enlargement 2nd to iodine deficiency
- Endemic cretinism- IQ reduction @ 15 points
- Goiter and thyroid cancers- potential causes of Horner’s syndrome
- Hashimoto’s thyroiditis- autoimmune destruction
Hypothyroidism: Symptoms

**EARLY SIGNS & SYMPTOMS: PRE-TREATMENT**
- Constipation
- Cold intolerance
- Fatigue or feeling tired
- Heavier menstrual periods
- Joint or muscle pain, cramps
- Paleness or dry skin
- Sadness or depression
- Thin, brittle hair or fingernails
- Weakness
- Weight gain without trying

**LATE SIGNS & SYMPTOMS: UNTREATED**
- Decreased taste and smell
- Hoarseness
- Puffy face, hands, and feet
- Slow speech
- Thickening of the skin
- Hair loss
Etiologies of Hypothyroidism

- Autoimmune disease - inflammation, destruction
  - Hashimoto’s disease
- Thyroidectomy - 1° for thyroid cancer, nodules
  - Radioactive iodine therapy for hyperthyroidism
- Head, neck radiation for unrelated conditions
- Disorders of thyroid hormone synthesis
  - Congenital (1 in 3000 infants defective, absent)

* #1 med for arrhythmia
Hashimoto’s Thyroiditis

- Most common cause of hypothyroidism
- Described 1912 Hakaru Hashimoto. MD
- Autoimmune disease
  - Antibodies bind to, mark TSH receptors
  - Lymphocytes infiltrate & ultimately destroy thyroid gland
- Gender: 5-10x more common in females
  - 3.5 females and 0.8 males per 1000 per year
Hashimoto's Thyroiditis: Histology

- Lymphocytic infiltration of the thyroid
  - Destruction of follicular epithelial cells, colloid
  - Reduction in colloid volume
  - Process eventually “burns out,”
  - Minimal, no functional thyroid remains
- Triggers - iodine, medications, infection, smoking, possibly stress

Colloid filled w/ inflammatory cells, mostly lymphocytes

Triggers - iodine, medications, infection, smoking, possibly stress
Signs & Symptoms
Pretibial Edema
Hypothyroidism: Understanding Laboratory Testing Results

- Lab Tests
  - T3 & T4 levels **reduced**
    - Why? Because inflamed thyroid tissues produce small amounts or no T3, T4 hormones
  - Thyroid stimulating hormone (TSH) **elevated**
    - Why? Because the feedback loop demands more thyroid hormones
# Interpreting Thyroid Lab Test Results

<table>
<thead>
<tr>
<th>Test</th>
<th>Lab Low</th>
<th>Optimal Range</th>
<th>Lab High</th>
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<tbody>
<tr>
<td>TSH</td>
<td>0.5</td>
<td>1.3-1.8</td>
<td>5.0</td>
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<tr>
<td>Free T4</td>
<td>0.8</td>
<td>1.2-1.3</td>
<td>1.8</td>
</tr>
<tr>
<td>Free T3</td>
<td>230</td>
<td>320-330</td>
<td>420</td>
</tr>
<tr>
<td>Free T3*</td>
<td>2.3</td>
<td>3.2-3.3</td>
<td>4.2</td>
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<tr>
<td>TSH</td>
<td>0.5</td>
<td>1.3-1.8</td>
<td>5.0</td>
</tr>
<tr>
<td>Sign or symptom</td>
<td>Affected patients (%)</td>
<td></td>
<td></td>
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<tr>
<td>----------------------------------</td>
<td>-----------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weakness</td>
<td>99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry or coarse skin</td>
<td>97</td>
<td></td>
<td></td>
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<tr>
<td>Lethargy</td>
<td>91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slow speech</td>
<td>91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eyelid edema</td>
<td>90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cold intolerance</td>
<td>89</td>
<td></td>
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<tr>
<td>Decreased sweating</td>
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<td></td>
<td></td>
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<tr>
<td>Cold skin</td>
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<td></td>
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<tr>
<td>Thick tongue</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Facial edema</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Coarse hair</td>
<td>76</td>
<td></td>
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</table>
Thyroid hormone replacement therapy
- Synthroid, Levoxyl
- Generics

Titrate dosing based on serum levels of unbound (free) T3, T4

Treatment may initially cause increased resting heart rate and elevate blood pressure

Important Signs of Hypothyroidism for OD’s to Recognize
- Lid edema, pretibial edema
- Changes in mentation, personality
- Moderate weight gain
- Changes in skin, hair

Often reversible
Thyroid Diseases: Hyperthyroidism

- Hyperthyroidism- excessive production T3 & T4
  - Increases overall metabolic rate
  - Incidence- 0.8 females/1000/year, 0.1 males/1000/year
- Graves disease (autoimmune thyrotoxicosis)
  - Most common cause- hyperthyroidism & goiter
  - Mediated by autoimmune stimulation (TSH receptor)
    - First described 1835- Dr. Robert Graves
- Goiter- enlarged thyroid gland
Signs & Symptoms of Hyperthyroidism

- Palpitations
- Heat intolerance
- Nervousness
- Insomnia
- Breathlessness
- Increased bowel movements
- Light or absent menses
- Fatigue
- Tachycardia
- Tremor
- Weight loss
- Muscle weakness
- Warm moist skin
- Hair loss
- Staring gaze
Signs of Hyperthyroidism

- Warm, moist skin
- Tachycardia (heart rate >85)
- Tremor
- Irregular heartbeat (atrial fibrillation)
- Muscle weakness
- Extraocular tissue inflammation*
- Proptosis*
- Pretibial myxedema*

*Graves disease only

Most common

Least common
Pathogenesis of Graves’ Disease

- Genetic predisposition a major factor!
- A thyroid-specific autoimmune disorder
- Plasma cells produce antibodies to the thyroid stimulating hormone receptor
Pathogenesis of Graves’ Disease

- Genetic predisposition a major factor!
- A thyroid-specific autoimmune disorder
- Plasma cells produce antibodies to the thyroid stimulating hormone receptor
- Antibodies bind to, continually stimulate thyroid gland to produce hormones
- Exogenous antibodies are not subject to negative feedback
- Unrestrained supply of thyroid hormone
Management of Hyperthyroidism

- Anti-thyroid medicines- only work in mild cases
  - Mechanism: reduce production of T3, T4
  - Methimazole (Tapazole)
  - Propylthiouracil (Propyl-Thyracil or PTU)
- Selenium supplementation
- Radioactive iodine (I-131) thyroid & radiation!
- Surgical ablation of thyroid
  - 1800s- mortality rate from thyroid surgery was @ 40%.
  - Injury to the recurrent laryngeal nerve- affects
Thyroid Associated Eye Disease (TAED)

- Dry eye (85%-95%)
- Thyroid-associated eye disease
  - Upper lid retraction (Dalrymple sign) #1 sign
  - Lower lid retraction
  - Proptosis
  - Compressive neuropathy
  - Visual field loss
  - Diplopia
  - Increased IOP – especially in up gaze
  - Reduction in venous flow to EOMs

Ocular manifestations of Graves' disease more common & severe in smokers ✪

Only a small percentage of patients w/ hyperthyroidism develop TAED
Patients w/ hypothyroidism have dry eye!

Patients w/ hyperthyroidism have dry eye!

How can that be?
Thyroid Associated Ophthalmopathy

- Upper lid retraction (Dalrymple sign) #1 sign
- Lower lid retraction
- Proptosis
- Compressive neuropathy
- Visual field loss
- Diplopia
- Increased IOP – especially in up gaze
- Reduction in venous flow to EOMs

Ocular manifestations of Graves' disease more common & severe in smokers ✪
What do These Patients Have In Common?

- Both have significant dry eye symptoms
- Both have significant staining with lissamine green
- 9 y/o female confirmed hypothyroidism

70 y/o male with history of hyperthyroidism
- Optic n. neuropathy, lid retraction, myopathy, visual field loss - smoker!

9 y/o female confirmed hypothyroidism
- Presents with symptoms of burning, blurring, stinging with near work
Evaluated 17 patients w/ Graves’ DZ
94% had dry eye symptoms
42% had increased tear film osmolarity
Increased palpebral fissure width (lid retraction)
Rose bengal staining \(\approx\) palpebral fissure width
Increased blink rate associated w/ Rose bengal staining

Thyroid Disease-Related Dry Eye

- Compared 48 subjects with thyroid-associated ophthalmopathy to 26 controls

Tests
- Tear production - Schirmer test
- Tear stability - TFBUT
- Ocular surface health - Rose Bengal staining
- Ocular surface health - fluorescein staining
- Ocular surface health - impression cytology (conjunctiva)
- Blinking - lid width, closure, ocular surface, upward excursion
- Lacrimal gland - expression of TSH receptors

## Thyroid Disease Related Dry Eye

<table>
<thead>
<tr>
<th>Test</th>
<th>TAO Patients</th>
<th>Controls</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schirmer</td>
<td>10 mm</td>
<td>17 mm</td>
<td>$p &lt; 0.001$</td>
</tr>
<tr>
<td>TFBUT</td>
<td>3 seconds</td>
<td>19.5 seconds</td>
<td>$P &lt; 0.001$</td>
</tr>
<tr>
<td>Rose bengal</td>
<td>2</td>
<td>0</td>
<td>$p &lt; 0.001$</td>
</tr>
<tr>
<td>Fluorescein</td>
<td>2</td>
<td>0</td>
<td>$p &lt; 0.001$</td>
</tr>
<tr>
<td>Impression cytology</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Blinking alteration sum</td>
<td>0.39</td>
<td>0</td>
<td>$p &lt; 0.05$</td>
</tr>
</tbody>
</table>

“A pathological engagement by autoantibodies of lacrimal TSH receptor could be an important factor in the alteration of the gland’s function and contribute to TAO and dry eye syndrome”

80% of all DES probably associated w/ MGD

PubMed search = 5 articles

T3 concentrates in MG

That's All Folks.
Managing Thyroid-Associated DED

- Well designed artificial tears
- Manage accompanying MGD
- Punctal occlusion after inflammation TX
- Xiidra- no data, based on mechanism, some benefit is likely
- Lacrisert- methylcellulose implant lower fornix
- Omega-3 + Omega-3 (GLA) fatty acids PO
Current OTC Dry Eye Therapy

- Contain various active and inactive agents
- Many preserved w/ BAK
- Patients view products as interchangeable
- Differing mechanisms of action and efficacies
- A need exists for clear patient education
Therapeutic Management of Thyroid-Associated Dry Eye + MGD

Lipid-Based Products

- Nature Made Odorless Fish Oil
- HydroEye
- Tears Again Advanced Eyelid Spray
- Systane Balance Lubricant Eye Drops
Therapeutic Management Thyroid-Associated Dry Eye + MGD

Procedures & Products
LipiFlow: Pressure + Pulsation for MGD

Therapeutic Management
Thyroid-Associated Dry Eye

Polyethylene Glycol and Propylene Glycol Products

Hypo-osmolar Products

Systane ULTRA Lubricant Eye Drops

Thera Tears Liquid Gel Lubricant Eye Drops
Biopsy: Dry Eye Dog

Conjunctiva

Lacrimal Gland

Pretreatment

CS-A

Posttreatment

CS-A
Cyclosporine

- Initially isolated from *Tolypocladium inflatum* soil in Norway
- Immunomodulator, not an immunosuppressant i.e., corticosteroids
- Acts on the immunophilin of immunocompetent lymphocytes, especially T-lymphocytes
- Inhibits calcineurin
- Responsible for activating the transcription of IL-2
- IL-2 activates T-helper lymphocytes → killer T-cells

Restasis Case Study: Sue

Sue, 65 yo female

- Hyperthyroidism w/ thyroidectomy
- Upper & lower lid retraction
- Va 20/20 – OU
- Meds: levothyroxine PO
- External
  - Lissamine green stain OU
  - Severely reduced tear meniscus
“a significant decrease (P < 0.01) in the mean score of the CsA group has also been shown at the end of the course.”

Xiidra binds to lymphocyte function-associated antigen-1 receptors on the surface of T cells.
May inhibit T-cell adhesion to ICAM-1 and secretion of inflammatory cytokines
Currently no studies specifically targeting Xiidra & thyroid-associated DED
Thyroid-associated Dry Eye & Punctal Occlusion

**Positive prognostic indicators**
- Moderate to adequate aqueous layer
- Minimal inflammatory indicators
  - Anterior blepharitis and or posterior blepharitis
  - Meibomian gland & lid margin scarring

**Negative prognostic indicators**
- Minimal to no aqueous layer
- Significant inflammatory indicators
  - Anterior blepharitis and or posterior blepharitis
  - Meibomian gland & lid margin scarring
  - Lid configuration issues
    - Punctal ectropion
Temporary Collagen Implants

- Excellent diagnostic tool
- Available in 0.3 and 0.4 diameters
- Use the largest size possible; dilate puncta if necessary to get maximum occlusion
- Dissolve in 3-5 days
- Occlude both lowers and uppers
- Phone progress 3-5 days- staff
Punctal Occlusion

Parasol/ Dome Style Plugs

- Available in bulk, non-sterile
- Can be loaded and disinfected prior to insertion
- Cost makes them very attractive
- 30-day replacement policy
- Design prevents rubbing of dome against conjunctiva in most cases.
- Available in small, medium, & large
Complications of Punctal Plugs

- Epiphoria
  - Remove one
  - Try flow restrictors
- Extrusion
- Canaliculitis
  - Dilation, irrigation, antimicrobial therapy
- Irritation
- Rubbing on conjunctiva
LACRISERT
(hydroxypropyl cellulose ophthalmic insert)

Indicated in patients with moderate to severe dry eye syndrome (DES), including keratoconjunctivitis sicca.

Indicated especially in patients who remain symptomatic after an adequate trial of therapy with artificial tear solutions.

Indicated for patients with exposure keratitis, decreased corneal sensitivity, and recurrent corneal erosions.

See www.lacrisert.com for an insertion guide and instructional video.
Gail- 48 y/o female with Graves disease, severe DES
- Lissamine green staining cornea & conjunctiva
- Severely reduced TBUT
- “Nothing really helped”
- Artificial tears
- Restasis
- Punctal plugs
- 1 month trial of Lacriserts
- “The best they have felt in yrs.”
- SLE: minimal staining,
Thyroid Associated Eye Disease (TAED)

- Characterized by inflammation in orbital tissues
  - Lymphocytic infiltration, edema, impaired glandular function
- Target tissues for thyroid autoimmune disease:
  - Thyroid gland
  - Extraocular muscles, orbital fat
  - Lacrimal gland
  - Pretibial skin
- Thyroid gland does **not** cause TAED
- Thyroid ablation may actually exacerbate TAED!
Mechanisms:
- Proptosis
- Upgaze restriction
- Fibrosis of the levator
- Contralateral ptosis (myasthenia)
- ↑ surface area ⇒ dry eye ⇒ lagophthalmos

Smoking strongly associated w/ poor prognosis!
Margin Reflex Distance

- Number of mm from the corneal light reflex to the lid margin

- Upper lid – 4 to 5 mm (rests slightly below limbus)

- Lower lid – 5 mm (rests at the lower limbus)

Reflected light to limbus – 2.5 mm

*Note palpebral aperture measurement is the same for examples A and D.

Fig. 2-5 The margin reflex distance.
CONCLUSION
Thyroid Disease: The OD’s Role

- **Detection**
  - High index of suspicion especially in females
  - Recent onset severe dry eye- no other cause
  - Weight gain, loss, pretibial edema
  - Changes in mentation, personality
  - Obvious changes in lids, adnexae

- **Consultation**
  - Internist or endocrinologist
  - Send reports after your visits: (Forms in MS Word)

- **Long-term care, reassurance, remediation**
Conclusion

- OD’s may be the first health care providers with the opportunity to detect thyroid disease
- ODs may be the first health care providers to diagnose TAED
- Management of most patients with these conditions within our scope and expertise
- Have an index of suspicion for any patient who presents with the diverse signs & symptoms of TAED