Metabolic Disease: Allopathic and Functional Treatments

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Disclosures: Tracy Offerdahl, PharmD

All relevant relationships have been mitigated

Dr. Offerdahl has the following financial disclosure:

- Non-salaried affiliation agreement with Pharmanex

Has not received any assistance from any commercial interest in the development of this course

The Cluster of Conditions

- Elevated glucose
  - Insulin resistance
  - ie >100 fasting or HbA1c >6.5
- High blood pressure
  - ie >120 systolic
- Obese/overweight
  - ie BMI >25
  - Abdominal obesity
- Abnormal cholesterol/ratios, dyslipidemia
  - High triglycerides ie > 150
  - Low HDL cholesterol ie <40
- Proinflammatory and prothrombotic states

3 of these 5 leads to:
Heart disease, stroke, DM, dementia, cancer…

Metabolic Syndrome

- A cluster of conditions that increase the risk of:
  - Heart disease
  - Stroke
  - Diabetes
  - Dementia
  - Cancer
    - Loves sugar
  - Polycystic ovarian syndrome
  - Non-alcoholic fatty liver disease

Diabetes Mellitus Pathophysiology Reminder

- **Type 1 DM**
  - Pancreatic beta cells are destroyed = subsequent severe or absolute lack of insulin
- **Type 2 DM**
  - insulin resistance in tissue
  - AKA a decrease in insulin sensitivity

Hemoglobin A1c

- A1c ≤ 6.5%
  - More "stable" patients
  - For patients without comorbidities
  - Low hypoglycemia risk
- A1c > 6.5%
  - Less "stable" patients
  - For patients with comorbidities
  - High hypoglycemia risk

Basic Mechanisms

- Type 2 Patients = primary dysfunction is hyperinsulinemia = insulin resistance
  - Insulin and insulin-secreting meds = hypoglycemia and weight gain
  - NEED MEDS that "re-teach" the body how to use the endogenous insulin that is already in the bloodstream!
  - All mechanism are NOT created equal!

Biguanide

Metformin (Glucophage)

- Initial Drug of Choice / Cornerstone of Therapy
- Stimulation of glucose uptake in peripheral tissues
  - Decreases insulin resistance = improves insulin sensitivity

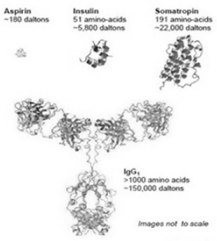
- Nausea, vomiting, diarrhea
- Weight neutral/SMALL amount of weight loss
- B12 deficiency
- Maybe other vitamin deficiencies?
  - Vitamin D
  - Other than GI, it is well-tolerated and VERY BENEFICIAL

Small Molecule Drugs versus Biologics

- Small molecule drugs are made by adding and mixing together known chemicals and reagents using a series of controlled and predictable chemical reactions (i.e. organic chemistry)
- Biologics are made by harvesting the substances produced and secreted by constructed cells (i.e. genetic engineering)

Biologic Drugs versus Small Molecule Drugs

- Biologic Drugs
  - Larger, complex, dynamic structures
  - Diverse populations of molecules
    - Not easily characterized
  - Complicated manufacturing
  - Example: Teprotumumab (Tepezza)
- Small Molecule Drugs
  - Synthetic
  - Manufactured using a defined chemical process
  - Smaller and simpler
  - Example: Aspirin



Monitoring Parameters Biologics

- **Biologics** are Immunomodulating/Immunosuppressive medications!
  - **HIGH immunogenicity** potential because they "tinker" with the immune system & come from nature
  - **Small molecule** drugs have LOW immunogenicity because they are synthetic
- Many of the systemic agents for autoimmune disease can cause significant morbidity and mortality!
  - Must place **PPD before initiating = if PPD**+, then initiation of a biologic may convert latent TB to ACTIVE tuberculosis
  - Once a biologic is initiated, watch for any signs or symptoms of infection
    - If the patient has a **"cold", "flu",** or is taking antibiotics
    - Then **biologic dose must be HELD** until the patient is healthy
  - FULL work-up for signs/symptoms of infection!
  - **ASK your patients about meds**!
  - We will look at the **diversity of the side effects** with these newer biologics

Why we use them…

- Autoimmune disease
  - **TED**, RA, psoriatic arthritis, **GCA**, PMR, **wet AMD**, macular edema, **uveitis, keratitis**, etc.
- Cancer
  - Which has an autoimmune component in many cases
  - More specific mechanisms of action
- With MANY of these diseases, patients OVER EXPRESS certain inflammatory mediators that contribute to their disease or condition!
  - TNF, IL, JK, T Cells, B Cells

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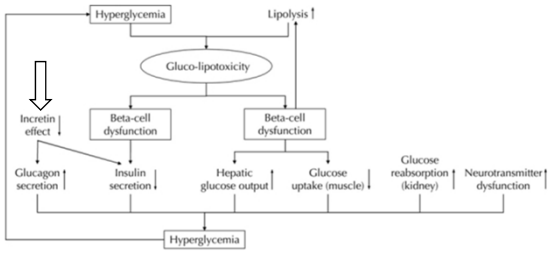
Why we use them…

- These highly sophisticated and "sexy" drugs treat medical conditions and diseases for which there may be no other treatment available!
- "Biosimilars" – 75% cheaper than reference product ("Biologic")

Are you familiar with the Incretin System?

Pathogenesis of hyperglycemia and Type 2 Diabetes



Rev Diabet Stud. 2011 Fall; 8(3): 323–338.
Published online 2011 Nov 10. doi: 10.1900/RDS.2011.8.323

Incretin mimetics - AKA glucagon like peptide 1(GLP-1) agonists

Exenatide injection (Byetta) –5Q injection = Bydureon

Liraglutide injection (Victoza)

Saxenda brand name = weight loss only

Abiglutide (Tanzeum)

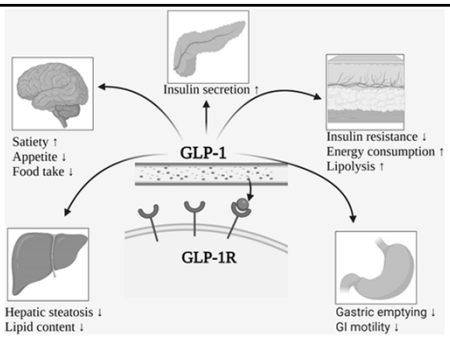
Dulaglutide (Trulicity)

Semaglutide (Ozempic) - SQ

Wegovy *brand name = weight loss – SQ*

Rybelsus *– T2DM and weight loss - PO*

Lixisenatide (Adlyxin)



https://www.frontiersin.org/articles/10.3389/fendo.2023.1085799/full

- **Brown fat**
  - ✶breaks down blood sugar and fat molecules to create heat and help maintain body temperature
  - ✶Cold temperatures activate brown fat, which leads to various metabolic changes in the body
- **White fat**
  - ✶Most of our fat
  - ✶stores extra energy
  - ✶Too much white fat builds up in obesity

Adverse Effects:

- Nausea and vomiting
- Hypoglycemia
- GI
  - Nausea, vomiting, diarrhea
  - "Frozen" gut
  - Pancreatitis
- Liraglutide
  - thyroid C-cell tumors
    - Contraindicated in patients with medullary thyroid cancer (active or PMH)
- GLP1 agonists in diabetic retinopathy?!?
  - 2018 data versus today…

FOCUS trial (How Semaglutide Compared to Placebo Affects Diabetic Eye Disease in People With Type 2 Diabetes)

- ✶ seeks to further investigate the long-term effects of semaglutide on DR in patients with T2DM diabetes
- ✶ measures the presence of early treatment diabetic retinopathy level progression in 1500 patients with an A1c between 7% and 10%
- ✶ 1 mg of semaglutide or placebo subcutaneously every week
- ✶ time frame of the trial will be 5 years and is estimated to be completed in early 2027

Good direction…

Until we get level 1 evidence from FOCUS trial

- ✶ recommended for docs to screen patients for DR before initiating semaglutide
  - on the basis of the stage of retinopathy, eye physicians and retina specialists need to discuss the risk benefit ratio in initiating the treatment

Tirzepatide (Mounjaro)

Tirzepatide, known as a 'twincretin', is a 'first-in-class' and the only dual glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) receptor agonist, that can significantly reduce glycemic levels and improve insulin sensitivity, as well as reducing body weight by more than 20% and improving lipid metabolism.

DPP4 Inhibitors (dipeptidyl-peptidase-4)

- **Sitagliptin (Januvia)** tablets
- **Sitagliptin + metformin (Janumet)**
- **Saxagliptin (Onglyza) tablets**
- **Linagliptin (Tradjenta)** tablets
- **Mechanism of Action**
  - Inhibits the breakdown of glucagon-like peptide-1 (incretin)

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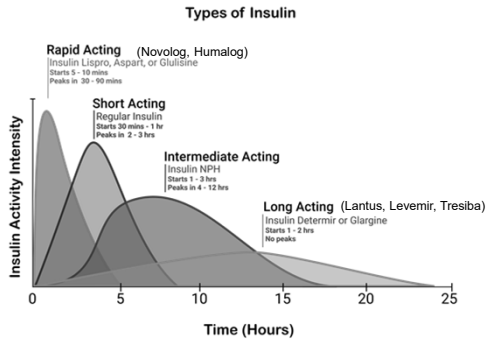
Sulfonylureas

- **MOA: S**timulate release of insulin from functioning pancreatic beta cells
- **2nd Generation Agents (preferred):**
  - glyburide (DiaBeta, Micronase, Glynase)
  - **glipizide (Glucotrol, Glucotrol XL)**
  - **glimepiride (Amaryl)**

Insulin Preparations

- Drug therapy of choice for all patients with type 1 DM and those with type 2 DM who cannot control their condition with diet, exercise, and 1st-line agents
  - Metformin
  - GLP-1 Agonists
  - DPP4 inhibitors
- **MOA: R**egulates glucose metabolism in the muscle and other tissues
- Semisynthetic "human" – identical amino acid composition to endogenous human insulin



Sodium-Glucose Co-Transporter 2 SGLT2 Inhibitor

- **Canagliflozin (Invokana)**
- **Dapagliflozin (Farxiga)**
- **Empagliflozin (Jardiance)**
- **MOA**
  - Inhibition of the SGLT2
    - Reduced absorption of filtered glucose
    - Lowering of renal threshold for glucose
    - Increasing of urinary excretion of glucose

Hypertension

- Very common comorbid condition
  - "compelling indication"
  - "JNC 8"
    - 8th Joint National Committee – prevention and treatment of hypertension
    - 2014
- Pretty big changes

Hyperlipidemia

- Common comorbidity in patients with diabetes
  - The "American triumvirate"
    - DM/metabolic syndrome, hypertension, hypercholesterolemia
- Statins are the only group of drugs that consistently decrease mortality in patients with high cholesterol!

Inflammation as a risk factor…

- CRP C-reactive protein
  - Marker for inflammation
  - Inflammation = increase in plaque formation
  - GCA, RA, celiac disease, DM, heart dz, food intolerances, obesity, etc.

Hyperlipidemia
Basic Treatment

- LDL – "bad cholesterol"
  - Drugs are usually the best choice
- HDL – "good cholesterol"
  - Protective
  - Exercise is the best treatment
- Triglycerides
  - Dietary changes and fish oil

Statins

- **MOA:** decrease LDL, decrease TGs, increase HDL

****ONLY AGENTS PROVEN TO LOWER THE RISK OF CV EVENTS in patients with high cholesterol**

Statin Treatment Table

Age	No Risk Factors	ASCVD Risk Factors	ASCVD
< 40 years old	No treatment	Mod/High Intensity dose	High Intensity dose
40-75 years old	Mod/High Intensity dose	High Intensity dose	High Intensity dose
> 75 years old	Mod/High Intensity dose	Mod/High Intensity dose	High Intensity dose

ASCVD= Atherosclerotic Cardiovascular Disease
Risk Factors: LDL ≥100mg/dL, hypertension, smoking, obesity, family hx of premature ASCVD

Moderate-Intensity Doses:
Rosuvastatin (Crestor) 5-10 mg
Atorvastatin (Lipitor) 10-20 mg
Simvastatin (Zocor) 20-40 mg
Pravastatin (Pravachol) 40-80 mg
Lovastatin (Mevacor) 40 mg
Fluvastatin (Lescol) 80 mg
Pitavastatin (Livalo) 2-4 mg

High-Intensity Doses:
Rosuvastatin (Crestor) 20-40 mg
Atorvastatin (Lipitor) 40-80 mg

Niacin

- Niaspan
  - Only other agent that decreases LDL, TG, and increases HDL
  - Not proven to decrease death
  - SEs:
    - Cutaneous flushing
    - GI problems (avoid in GERD or PUD)
    - Hyperuricemia
    - Loss of glycemic control in DM

Fish Oil

- **OTC AND Prescription Options**
- Ethyl Ester: DHA and EPA
  - It is ALL about the chemistry!
    - Ethyl-ester omega-3
    - Cheaper to make because it requires LESS purification to remove an alcohol side-chain
      - ALL RX products are this!
  - More likely to give "fishy" burps and aftertaste
  - We are learning that we might have to give a BIGGER dose of EE formulations to get the same "job" done as a lower dose of more PURE formulations or those that are the next BIOTRANSFORMATION step!

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Prescription and OTC Options
Ethyl Ester Products

- Prescriptions options
  - Lovaza® (omega-3 ethyl esters) 4g/day
    - FDA-approved to lower triglyceride levels in hypertriglyceridemia
  - Vascepa ® (icosapent ethyl)- 4g/day
    - FDA-approved to lower trigylceride levels in hypertriglyceridemia
- Recommendations:
  Typically given 1 capsule 3 – 4 times per day (with food)

Fish Oil

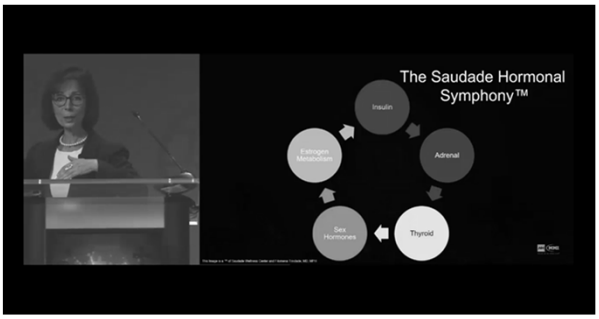
OTC Options

- Triglyceride: DHA and EPA
  - Purified product because an extra step of purification removes the alcohol side-chain = better absorption
  - "you get what you pay for?...We THINK!?"
  - Less likely to cause fishy side effects

Dosing: General Recommendations

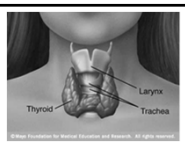
- For general health benefits:
  - 1,500 – 2,000 mg of EPA + DHA in 1-3 divided doses
- For auto-immune disease/anti-inflammatory:
  - 4,000 mg of EPA + DHA daily in divided doses
  - Close follow-up evaluation is necessary
- BUT…EPA/DHA do not have RESOLVENT activity without being biotransformed (ie into SPMs)

Thyroid Disease and Thyroid Eye Disease



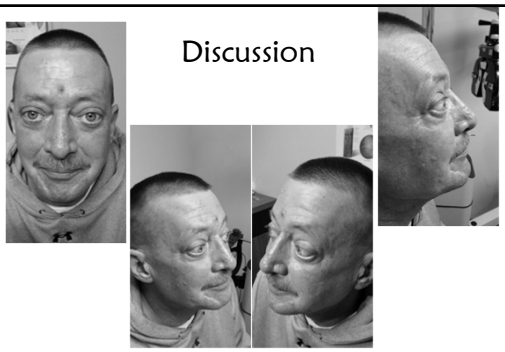
Credit to: Filomena Trindade, MD

Thyroid

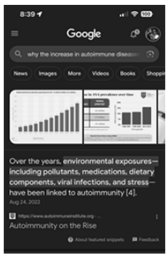


- Largest endocrine gland in the body
- Butterfly shaped
- Two lobes located on either side of the trachea in the lower portion of the neck
- Lies just below skin and muscle layer surface
- The thyroid is controlled by the hypothalamus and pituitary
- The primary function of the thyroid is production of the hormones thyroxine (T4), triiodothyronine (T3), and calcitonin

Discussion



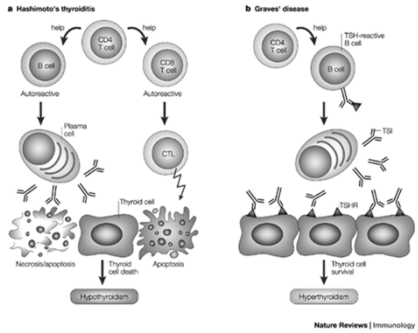
Why Autoimmune Disease is on the Rise?



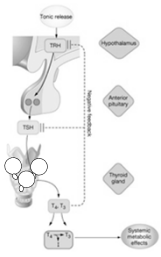
Antibodies of Thyroid Dysfunction

- 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



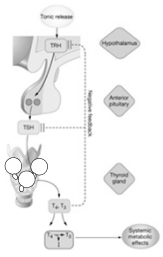
Hyperthyroid



- TSI attacks the thyroid

- T3 and T4 increase
- TSH decreases

Hypothyroid



- TBAb attacks the thyroid

- T3 and T4 decrease
- TSH increases

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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

GRAVE'S
(Hyperthyoidism)

- 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)

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

Autoimmune atrophic thyroiditis
(Hypothyroidism)

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

Postpartum Thyroiditis
(Hypothyroidism)

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

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
  - Microcyticanemia
  - Possible goiter
  - Myxedema

Systemic Manifestations of Hypothyroid
(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

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

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

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

Why is this so confusing?

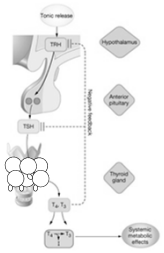
- Eye disease may be brought on by thyroid dysfunction
  - Successful treatment of the thyroid gland does not guarantee that the eye disease will improve
  - No particular thyroid treatment can guarantee that the eyes will not continue to deteriorate
  - Once inflamed, the eye disease may remain active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

Thyroid Eye Disease

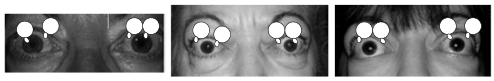
- What causes the Thyroid Eye Disease signs and symptoms?
- The high and low levels of T3 and T4
- The antibodies that are attacking the thyroid gland

Euthyroid Graves' disease

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



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



General Ocular Symptoms

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

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

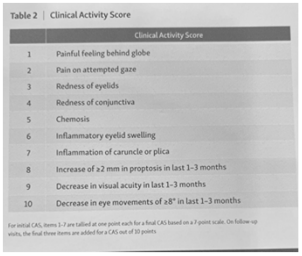


Table 2 | Clinical Activity Score

	Clinical Activity Score
1	Painful feeling behind globe
2	Pain on attempted gaze
3	Redness of eyelids
4	Redness of conjunctiva
5	Chemosis
6	Inflammatory eyelid swelling
7	Inflammation of caruncle or plica
8	Increase of ≥2 mm in proptosis in last 1–3 months
9	Decrease in visual acuity in last 1–3 months
10	Decrease in eye movements of ≥8° in last 1–3 months

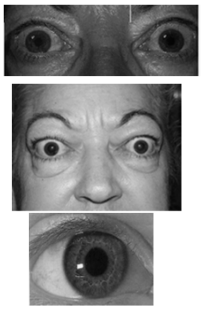
For initial CAS, items 1–7 are tallied at one point each for a final CAS based on a 7-point scale. On follow-up visits, the final three items are added for a CAS out of 10 points

Lid Involvement

- Lid Retraction
- Lid Lag
- Lagophthalmus

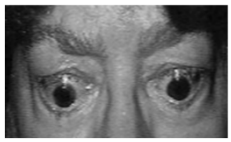
Lid Retraction

- 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



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



Lagophthalmos

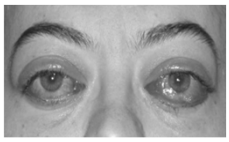
- Inability to form a complete lid closure with a normal blink due to Exophthalmos/ Proptosis
- Often leads to corneal exposure

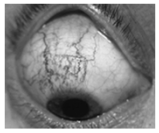
Soft Tissue Involvement

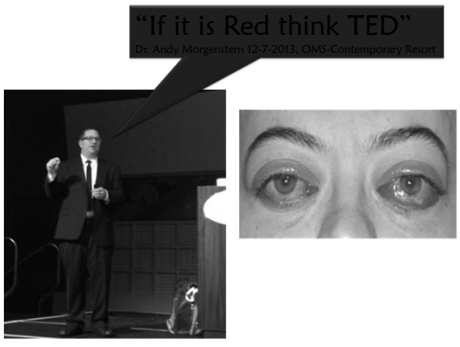
- Conjunctiva
- Chemosis
- Periorbital edema

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

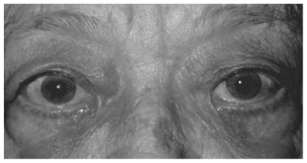






Periorbital Edema

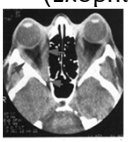
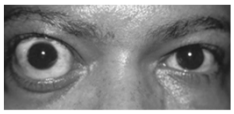
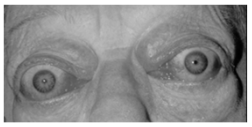
- Inflammation of the subcutaneous connective tissue
- May be first sign of thyroid eye disease
- Greatest in the morning



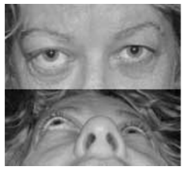
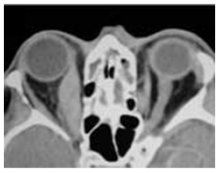
Infiltrative Orbitopathy
(Exophthalmos/Proptosis)

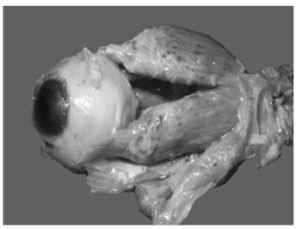
- Thyroid Eye Disease is most common cause of unilateral and bilateral exophthalmos
- The term exophthalmos is reserved for prominence of the eye secondary to thyroid disease
- May need MRI to determine or obvious exophthalmos may be present
- It is permanent in 70% of cases
- Caused by increased volume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

Infiltrative Orbitopathy
(Exophthalmos/Proptosis)

Infiltrative Orbitopathy
(Exophthalmos/Proptosis)


© Elsevier 2005

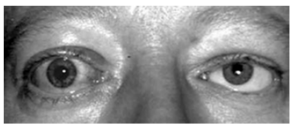
Exophthalmometry

- 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

Restrictive Myopathy

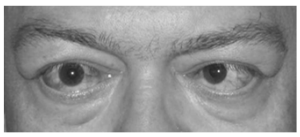
- Secondary to edema and fibrosis of EOM's
- Inferior Rectus (IR) muscle is most commonly involved
- Occurs in 30-50% of patients
- Diplopia may be transient but in 50% it's permanent



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

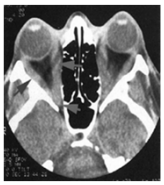
Restrictive Myopathy



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

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



Treatment of Thyroid Eye Disease

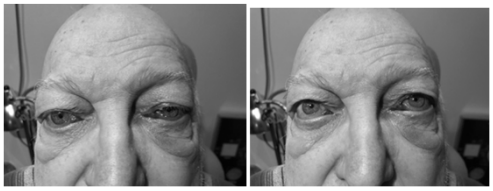
- Palliative (hormone imbalance, active, passive)
  - Lubricants
  - Topical anti- inflammatory (Lotemax/Restasis)
  - Prisms
- Steroids (active phase)
  - Orals
  - Peri-ocular injections
  - IV with oral steroid taper
- Orbital radiotherapy (active phase)
- Orbital Decompression (passive phase)
  - 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

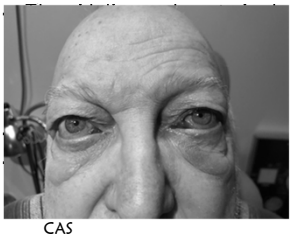
Smoking causes treatments to be less effective

February 25, 2019

"Nothing Else Can Be Done"



Clinical Activity Score (CAS)



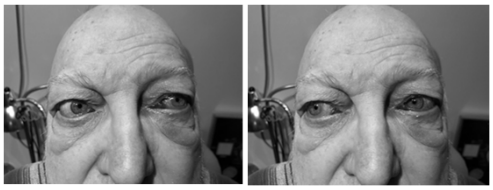
CAS

Table 2 | Clinical Activity Score

	Clinical Activity Score
1	Painful feeling behind globe
2	Pain on attempted gaze
3	Redness of eyelids
4	Redness of conjunctiva
5	Chemosis
6	Inflammatory eyelid swelling
7	Inflammation of caruncle or plica
8	Increase of ≥2 mm in proptosis in last 1–3 months
9	Decrease in visual acuity in last 1–3 months
10	Decrease in eye movements of ≥8° in last 1–3 months

For initial CAS, items 1–7 are tallied at one point each for a final CAS based on a 7-point scale. On follow-up visits, the final three items are added for a CAS out of 10 points

February 25, 2019
"Nothing Else Can Be Done"



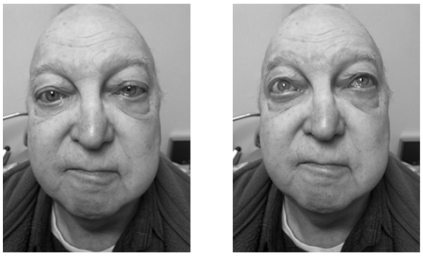
February 25, 2019
"Nothing Else Can Be Done"

March 1, 2019 (4 days later)
Oral and Topical Steroids

March 1, 2019 (4 days later)
Oral and Topical Steroids

March 1, 2019 (4 days later)
Oral and Topical Steroids

March 25, 2019



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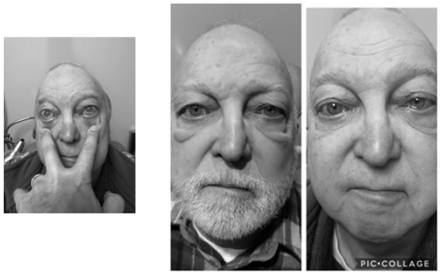
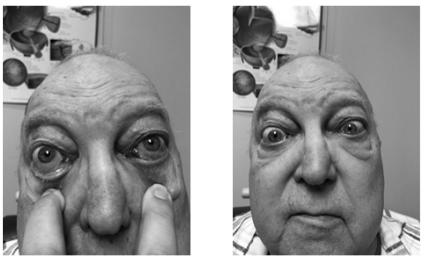


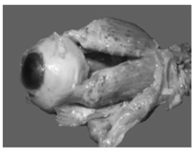
April 22, 2019



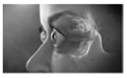
April 22, 2019

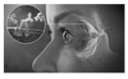
Teprotumumab-trbw (Tepezza)

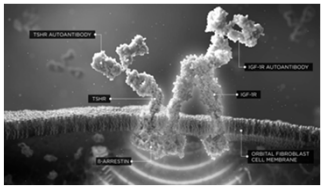
- Horizon Therapeutics – HQ Dublin, Ireland and US based Chicago
- Biologic pharmaceutical
  - Chinese Hamster Ovary
  - Infusion, 8 total, every 3 weeks
- Thyroid eye disease
  - IGR-1 (Insulin like growth factor 1) and TSH receptors are over expressed
- IGF-1 receptor inhibitor monoclonal antibody
  - On the orbital fibroblasts
    - Inhibiting downstream inflammatory cascade
      - Cytokines, hyaluran, 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

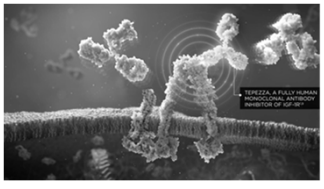


Teprotumumab-trbw (Tepezza)









https://www.tepezza.com/hcp/tepezza-moa/

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
  - Immunomodulary
    - Tepezza
      - IGF-1R inhibitor
      - Full humanized monoclonal antibody
        - All the proteins are human – less to no sensitivity – more focused effect
      - Obital 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

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

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.

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

Teprotumumab-trbw (Tepezza)

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

Biologics Used Off Label for TED

Table 1 | Biologic therapies for TED

Small Molecule Therapies	Target	Dosing	Findings	Side Effects
Rituximab	CD20	2 infusions of 1000 mg each 2 weeks apart	Mixed results in improvement of CAS, proptosis, and motility	Exacerbation of inflammatory bowel disease, arthralgias, hypotension
Adalimumab	TNF-α	Subcutaneous injections of initial 80 mg dose, then biweekly 40 mg doses for a total of 10 weeks	6/10 showed decrease in inflammation, no changes in proptosis or extraocular motility	Sepsis (1/10)
Infliximab	TNF-α	Infusions at 5 mg/kg each dose over 2 hours	Case reports showed improvement in visual acuity and CAS after 1 dose and complete resolution in 3 cases after 3 doses	Infections, malignancies (especially lymphoma), drug-induced lupus
Tocilizumab	IL-6	3 infusions at 8 mg/kg given every 4 weeks	93% with ≥2-point improvement in CAS, mean proptosis reduction of 1.5 mm, no change in diplopia	High recurrence rate, transaminitis, pyelonephritis
Teprotumumab	IGF-1R	Initial infusion at 10 mg/kg, followed by 7 infusions at 20 mg/kg given every 3 weeks	Reduced proptosis in 79–83% of patients, improved CAS in 69%, reduced diplopia in 68%	Most common: muscle spasms, fatigue, nausea, diarrhea, hyperglycemia, hearing impairment, and alopecia. Between 5% and 12% with serious adverse events requiring early withdrawal

CAS, Clinical Activity Score; CD, cluster of differentiation; FcRn, neonatal Fc receptor for immunoglobulin G; IL, interleukin; TNF, tumor necrosis factor.

Additionally, multiple case reports published since

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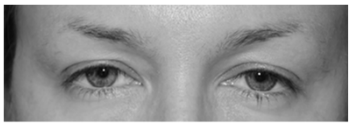
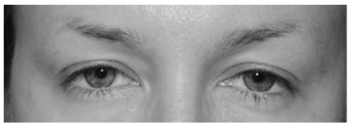
Optometry's Opportunity



Eyelash and Brow Loss

- Hypothyroidism or hyperthyroidism, hair loss can be an unfortunate side effect
- Dry, brittle hair, thinning on the scalp, and even loss of lashes and brows
- Some drugs used to treat thyroid conditions can also contribute to the loss of hair
- Left untreated, the hormonal changes associated with hypothyroidism or hyperthyroidism can completely stop new hair strands from developing

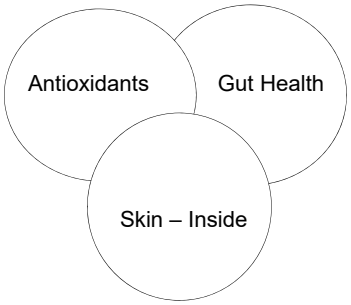


Functional Interventions

Immune System Support
Gut Microbiome Support

Credit to: James LaValle, RPh, CCN

Optometry's Opportunity
Optom-Portunity



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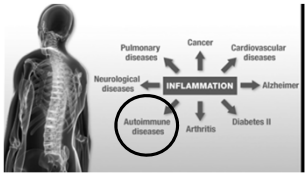
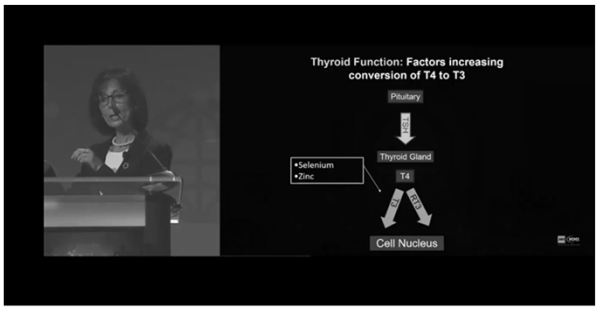
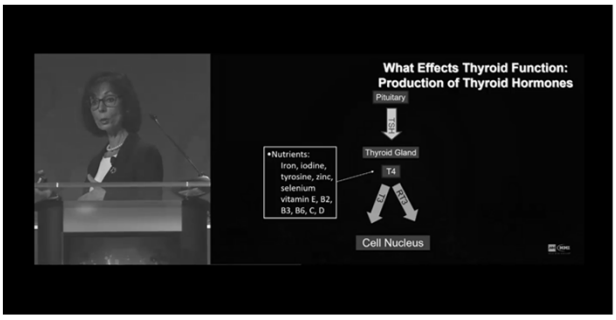
Chronic and Low-Grade Inflammation

Like cancers and other slow-burn diseases, identifying these conditions early can make the difference between full recovery or a dramatically reduced quality of life or even death (vision loss or blindness)





Credit to: Filomena Trindade, MD



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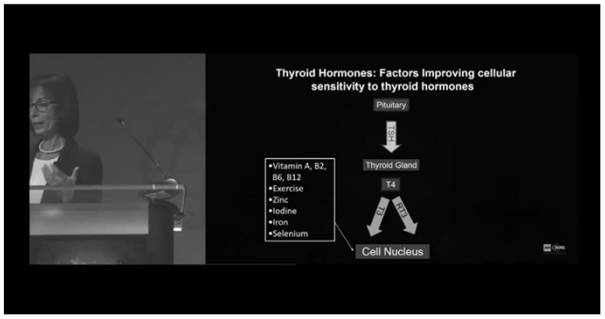

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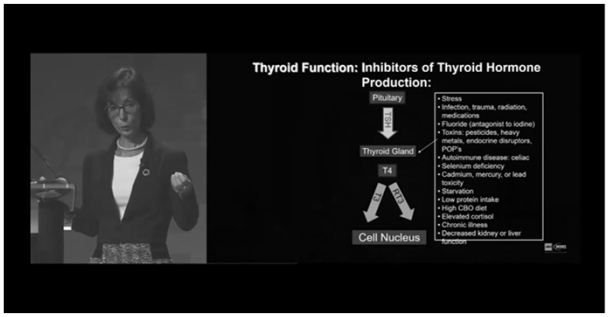

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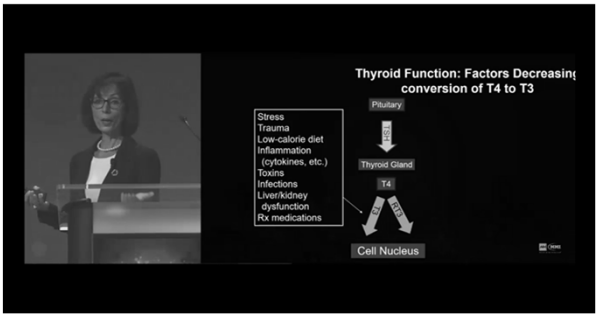


Credit to: Filomena Trindade, MD

Skin Carotenoid Levels
Oxidative Stress/Inflammation/Anti-Oxidant Deficient

- **Quick Test (approx. 30 sec)**
- **Portable**
- **Cost Effective**
- **Remeasure in 60 days**
- **Reassurance to you and patient**

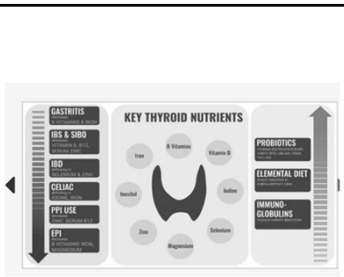
Ingredients

Ingredients	Amount	% Daily Value
Serving Size: 1 Packet		
Vitamin A (83% as Beta Carotene (1875 mcg RAE) from *Blakeslea trispora*, and Vitamin A palmitate) (375 mcg RAE)	2250 mcg RAE	250%
Vitamin C (as Calcium Ascorbate)	200 mg	222%
Vitamin D (as Cholecalciferol)	5 mcg (200 IU)	25%
Vitamin E (as D-Alpha-Tocopheryl Acetate, D-Alpha Tocopherol, Tocotrienols)	50.3 mg	335%
Vitamin K (as Phytonadione)	20 mcg	17%
Thiamin (as Thiamine Mononitrate)	3.75 mg	313%
Riboflavin (as Riboflavin)	4.25 mg	327%
Niacin (as Niacinamide)	47.5 mg NE	109%
Vitamin B6 (as Pyridoxine Hydrochloride)	5 mg	294%
Folate	500 mcg DFE (300 mcg folic acid)	125%
Vitamin B12 (as Cyanocobalamin)	15 mcg	625%
Biotin (as Biotin)	75 mcg	250%
Pantothenic Acid (as D-Calcium Pantothenate)	15 mg	300%
Calcium (as Calcium Carbonate, Di-Calcium Malate, Calcium Ascorbate)	250 mg	19%
Calcium (as Calcium Carbonate, Di-Calcium Malate, Calcium Ascorbate)	250 mg	19%
Iodine (as Potassium Iodide)	50 mcg	33%
Magnesium (as Magnesium Glycinate, Magnesium Oxide)	225 mg	80%
Zinc (as Zinc Bisglycinate)	75 mg	68%
Selenium (as L-Selenomethionine, Sodium Selenite)	70 mcg	127%
Copper (as Copper Bisglycinate)	0.5 mg	56%
Manganese (as Manganese Bisglycinate)	1 mg	43%
Chromium (as Chromium Nicotinate Glycinate)	100mcg	286%
Molybdenum (as Molybdenum Bisglycinate)	375 mcg	83%
Polyphenol and Flavonoid Blend	975 mg	†
Catechins (from *Camellia sinensis Leaf* Extract)	145 mg	†
Quercetin	125 mg	†
Grape Seed Extract (min. 95% Polyphenols)	112.5 mg	†
Citrus Bioflavonoids (from Citrus Fruits)	62.5 mg	†
Resveratrol (from *Polygonum cuspidatum* root extract)	62.5 mg	†
Mixed Tocopherols (Gamma, Delta & Beta Tocopherols)	53 mg	†
Alpha-Lipoic Acid	15 mg	†
Inositol (as Inositol)	5 mg	†
Carotenoid Blend	3.5 mg	†
Lycopene (as Lycopene)	2.5 mg)	†
Lutein (from Marigold Flower Extract)	1 mg)	†
Boron (as Boron Citrate)	1.5 mg	†
Vanadium (as Vanadyl Sulfate)	10 mcg	†

OTHER INGREDIENTS: Gelatin, Microcrystalline Cellulose, Crosmarmellose Sodium, Stearic Acid, Magnesium Stearate, Silicon Dioxide, Titanium Dioxide.

CONTAINS: Fish (Cod, Pollack, Haddock, Hake, Cusk, Redfish, Sole, Flounder).

Credit to: James LaValle, RPh, CCN



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Thank you!

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