Thyroid Health

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Goals for this presentation

- Review thyroid physiology, nutrition, and symptoms of imbalance
- Describe thyroid function within a larger relational framework
- Demonstrate the effects of lifestyle on thyroid function
- Survey approaches to treatment within this larger context

Perspective for this presentation

Holistic

Alternative

Complementary & Alternative

Integrative

Green Pharmacy

Naturopathic

Functional Medicine

Systems Biology

Systems Biology

‘While most researchers continue to break down disease into smaller and smaller pieces in an effort to understand how they work, systems biologists take the opposite approach by looking at how all the pieces of a system interact—be it at the level of the population, organism, tissue, or cell—and then put the pieces together. Systems biology is a conceptual framework that researchers use to further understand complex biological processes.’

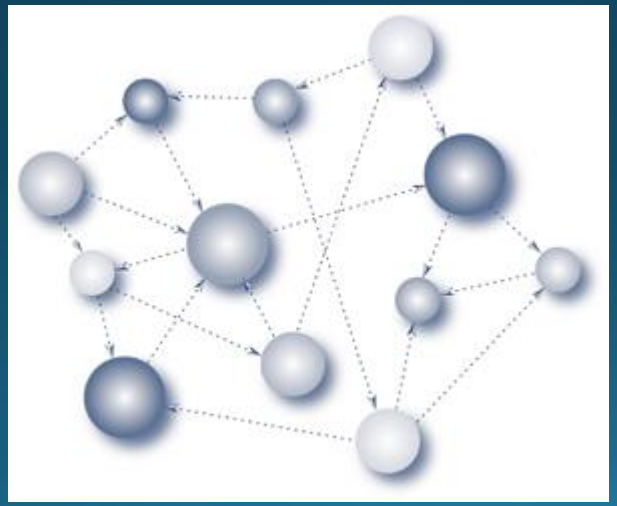
NIH National Centers for Systems Biology (NCSB)

Using a perspective that can describe the condition

- Chronic illnesses generally arise out of the the interplay of multiple factors over a long period of time.
- While the chronic illness may manifest similar symptoms in most people
  - Standardized treatment is not consistently successful in all patients
  - Focusing on the similarity of symptoms in order to diagnose and treat may miss underlying causes that lead to more effective treatment
  - What we may call chronic disease may be symptoms of larger system imbalance that may return to homeostasis with a comprehensive understanding and intervention.

Broadening our perspective

- Standard view: Hypothalamus-Pituitary-Thyroid Axis
- Emerging view: Genetic - Epigenetic - Psychologic - Hypothalamic - Pituitary - Adrenal - Gonadal - Thyroid - Immunologic - Microbiome - Community – Environmental System



To not get lost in the web, let's start with the thyroid

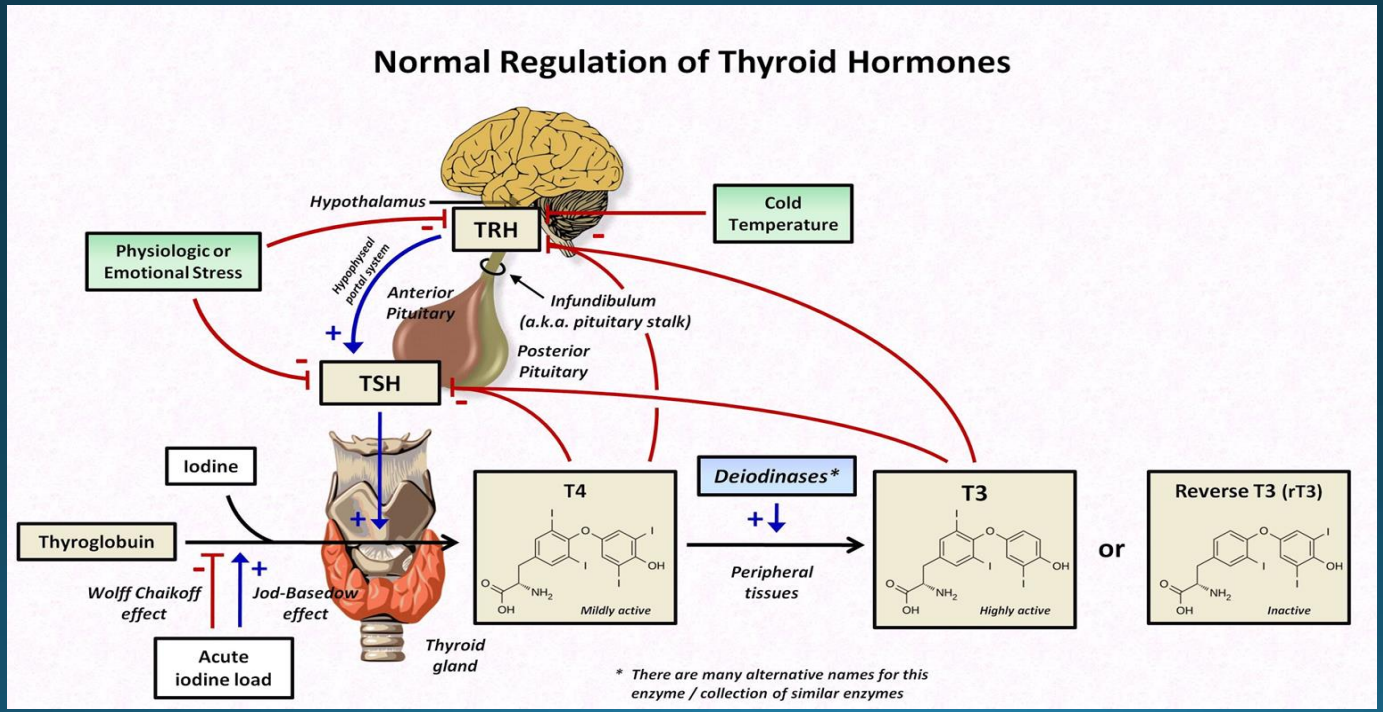
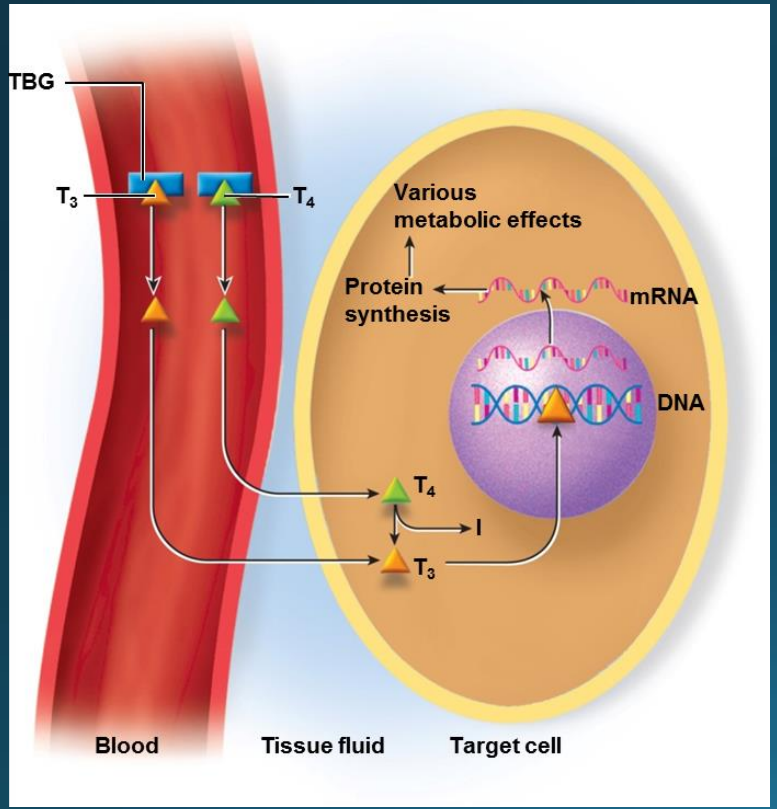


Image credit: Strong Medicine

Thyroid hormone in the blood and cell



Thyroid hormone (T_4/T_3) is predominantly bound to thyroid binding globulin (TBG.)

Various influences including medications and increased estrogen can increase TBG, thus decreasing the free fraction of Thyroid hormone available to stimulate the thyroid receptor.

Thyroid Disease Statistics

- 27 Million Americans estimated to suffer from Thyroid Disease.
- 13 Million Americans estimated to suffer from undiagnosed Thyroid Disease
- 14 Million Americans estimated to be affected by Hashimoto's Thyroiditis
- 8 out of 10 patients with Thyroid Disease who are women.

American Association of Clinical Endocrinologists (AACE)

Thyroid Disease Symptoms

- **Hyperthyroid-** heart palpitations, heat intolerance, anxiety, exopthalmos, photophobia, diplopia, insomnia, diarrhea, weight loss, tremor, sweating, skin thinning, brittle hair.

- **Hypothyroid-** slowed heart rate, cold intolerance, depression, fatigue, dry skin, hoarseness, puffy face, high cholesterol, constipation, goiter, muscle aches/stiffness/weakness, thinning hair, irregular periods, impaired memory, myxedema.

Thyroid hormone affects all organ systems and the effects can be beyond the standard symptoms. Subclinical Hypothyroidism may be difficult to diagnosis because of the diverse array of potential symptoms.

Differentiating Types of Thyroid Disease

Assessment is made by a thorough history, clinical exam, and laboratory values. Because laboratory values have normal ranges, always consider the patient. Testing is guided by clinical suspicion and may include:

- Primary Hyper/Hypothyroidism is at the level of the thyroid gland
  - May be from an overactive thyroid nodule
  - May have many underlying causes such as poor nutrition
- Central Hypo/Hyperthyroidism is at the the level of the Hypothalamus/Pituitary
  - May be due to:
    - Loss of responsiveness to a feedback loop
    - Tumor
    - Damage to the gland (CVA, toxin, radiation, inhibitor, TBI, etc.)

Subclincal Hypthyroidism (SCH)

Symptomatic with TSH and free T_4 within range

- Fatigue (mental and physical)
- Weight gain
- Cardiovascular dysfunction
- Dyslipidemias
- Atherogenesis
- Glucose intolerance/insulin resistance
- Poor pregnancy outcomes

Wartofsky L, et al. Overt and 'subclinical' hypothyroidism in women. Obstet Gynecol, Surv. 2006 Aug;61(8):535-42.

Do you treat SCH?

Six recent meta-analyses suggest that SCH is associated with:

- A cardiovascular risk for persons younger than age 70
- No effect for those aged 70 to 80
- A possible protective effect for those older than 80

Biondi B. Cardiovascular effects of mild hypothyroidism. Thyroid 2007;17(7):625-630.

Recent New England Journal of Medicine

- Levothyroxine provided no apparent benefits in older persons with subclinical hypothyroidism

Autoimmune Thyroid Disease (AIT)

- Autoimmune Hyperthyroid (Graves Disease)
  - Elevated Thyroid Stimulating Antibodies
  - Symptoms fluctuate with level of antibodies

- Autoimmune Hypothyroid (Hashimotos Thyroiditis)
  - Anti-Thyroperoxidase Antibodies and Anti-Thyroglobulin Antibodies
  - The symptoms may fluctuate depending on the level of antibodies. Hashimotos may have temporary surges of thyroid hormone released if the immune attack increases.
  - It is a common cause of hypothyroidism in the US affecting women seven times more than men. (Up to 20% of menopausal women, 24% of allergic women, and 5–10% of postpartum women)

Wilson's Low Temperature Syndrome

- This condition is not recognized by the American Thyroid Association (ATA). Dr. E. Denis Wilson theorized that the condition is the result of intracellular complications of utilizing thyroid hormone or converting T4 into T3. He stated that patients will have a low basal body temperature (below 98.6F) and diffuse symptoms of hypothyroidism. Wilson advised a sustained release T3 formulation for treatment.

- There have been reported severe complications for treating these symptoms with thyroid medication. Given that symptoms of hypothyroidism are so broad, it is worth investing all underlying causes. The ATA determined that the mean waking body temperature is 97.5F and that the diagnosis of the condition by basal body temperature could lead to a dangerous over prescribing of T3.

De-what? And my Gut?

T_4 is more of a precursor hormone and has a ½ Life of 7 days. T_3 is the 'active' form and has a ½ Life of 1 day. The body has 3 deiodinases that convert T_4 into either T_3 or reverse T_3 (D1, D2, and D3.)

- D1 is predominantly expressed in the liver, kidneys, and thyroid
- D2 is predominantly expressed in the brain, anterior pituitary, thyroid, and to some extent in skeletal muscle
- D3 is predominantly expressed in the brain, skin, liver, and intestines. It converts T_4 to reverse T_3.

D1-3 deiodinases require selenium for production and iron as a cofactor. D2 and D3 are less affected by selenium deficiency than D1. D1 in the liver is primarily responsible for plasma T_3.

Oxford Textbook of Endocrinology and Diabetes (p314-316)

Conversion & Delivery

Many factors can induce or inhibit the deiodinase enzymes and affect the conversion of T_4 to either T_3 or reverse T_3.

T_3 is the 'active' thyroid hormone while reverse T_3 has a counter effect. Reverse T_3 is not stimulatory and can bind the thyroid receptor. You can think of it as a response to stress/infection/inflammation that slows you down to help you survive.

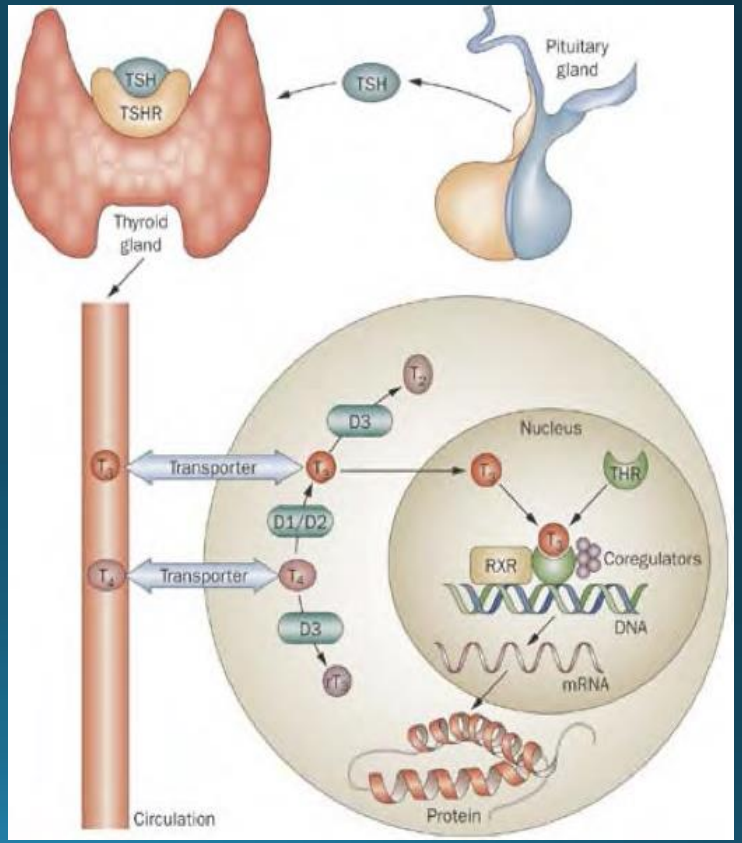


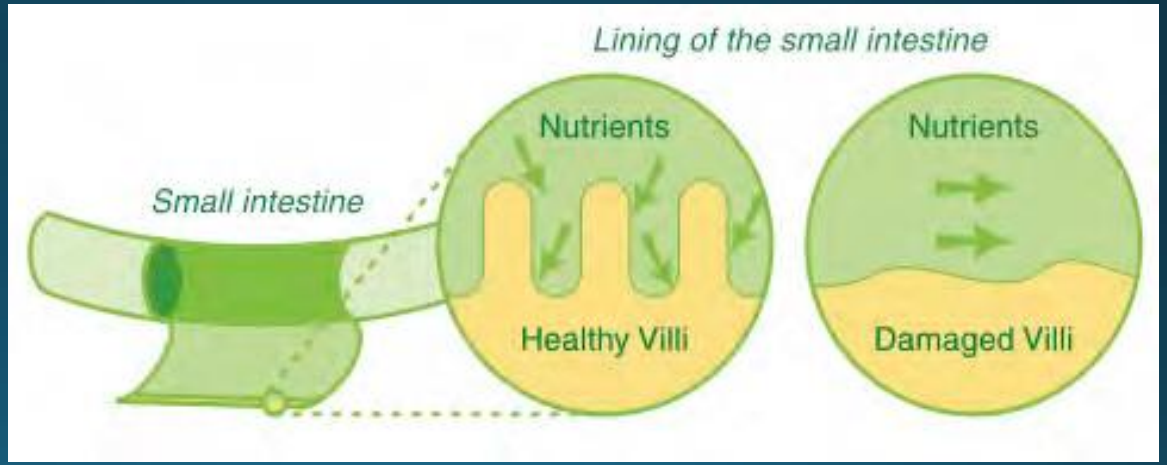
Image credit: Nat Rev Endocrinol

D1/D2 inhibitors that slow the conversion of T4->T3

- Certain medications
- Selenium deficiency
- Inadequate protein, excess carbohydrates
- Chronic inflammation and illness (cytokines, free radicals)
- Compromised liver or kidney function
- Cd, Hg, Pb, herbicides, pesticides
- Stress (emotional or physiological), i. e, excess cortisol, catecholamines
- Excess estrogen
- RT3

Conditions affecting nutrient absorption affect Thyroid

- Iron
- Zinc
- Folic acid
- B12
- Calcium
- Selenium
- Vitamin A
- Vitamin D
- Vitamin E
- Vitamin K



Other effects… to demonstrate complexity

- A small portion of T_4 is also converted into thyroamines which can act like neurotransmitters. They can exert 'acute and dramatic effects…inducing a torpor-like state.' These are then converted by MAO enzymes to forms which may have stronger affinity than T_3.
- Another portion is converted via sulfation or glucuronidation (phase II detoxification)
  - The phase II detox pathway increases solubility for excretion.
  - Barbituates, fibrates, PCBs, and some antiepileptics increase glucuronidation of T_4
  - Bacterial sulfatases and beta-glucuronidases in the intestine can liberate the iodothyronines and thus create an enterohepatic cycle. Intestinal health influences this cycle.
  - All of these factors influence the amount of free T_3

Oxford Textbook of Endocrinology and Diabetes (p314-316)

Goitergens

Goitrogens: substances that disrupt the production of thyroid hormones by interfering with iodine uptake in the thyroid gland

- Brassica/Cruciferous Vegetables
- Peanuts
- Pearl Millet
- Strawberries
- Peaches
- Spinach
- Sweet Potatoes
- Bamboo shoots
- Others…

Common Medications that slow conversion of T4 to T3

- Beta blockers
- Birth control pills
- Estrogen replacement
- Lithium
- Phenytoin
- Theophylline
- Chemotherapy

Other medications and pathways…

Inhibition of levothyroxine absorption
Iron
Calcium
Aluminum hydroxide
Colestyramine
Colestipol
Sucralfate
Raloxifene

Increased hepatic metabolism
Phenobarbitol
Phenytoin
Carbemazepine
Rifampin
TKI (Imatinib, axitinib, motesanib, vandetanib)
Rexinoids

Best Pract Res Clin Endocrinol Metab. 2009 Dec; 23(6): 793–800

Inhibition of T4/T3 synthesis
Propylthiouracil
Methimazole

Inhibition of T4/T3 secretion*
Lithium
Iodide
Amiodarone
Aminoglutethimide

Thyroiditis
Interferon
Interleukin-2
Amiodarone
Sunitinib

TSH suppression
Glucocorticoids
Dopamine agonists
Somatostatin analogs
Rexinoids
Carbemazepine
Oxcarbemazepine
Metformin

Decrease hepatic metabolism
Metformin[2]

Inhibition of 5′ deiodinase
Propylthiouracil
Methimazole
Propranolol
Glucocorticoids
Iodide

Increased thyroxine binding globulin levels
Estrogen
Raloxifene
Tamoxifen
Methadone
Mitotane
Fluorouracil

Decreased thyroxine binding globulin levels
Androgens
Glucocorticoids
Nicotinic acid

Toxins can affect thyroid function

Thyroid Disruptors	Mechanism	Effect
Perchlorates, thiocyanate, nitrate, bromates, phthalates	Blocking uptake of iodide into thyroid cell	Decreased synthesis of T3 and T4
Methimazole, amitrole, soy isoflavones, benzophenone 2	Blocking production of TPO in thyroid follicles	Decreased synthesis of T3 and T4
PCBs, pentachlorophenol, flame retardants, phthalates	Competitive binding to thyroid transport protein (TTR)	Possible effect on fetal brain T4 production
Dioxin, PBDE, chlordane	Altering transport across cell membrane	Increased biliary elimination of T3 and T4
Acetochlor (herbicide), PCBs	Enhanced hepatic metabolism	Increased biliary metabolism of T3 and T4
PCBs, triclosan, pentachlorophenol, dioxin, difuran	Inhibition of sulfation	Decreased sulfation of thyroid hormones leading to possible decrease of peripheral T3 synthesis
FD&C red dye #3, PCBs, octyl-methoxycinnamate	Inhibition of deiodinase activity	Decreased peripheral T3 synthesis
PCBs, bisphenol A, hexachlorobenzene, flame retardants	Altering binding to thyroid receptor	Altered thyroid hormone directed gene transcription
DDT, PCBs	Inhibiting TSH receptor	Decreased production of T3 and T4

Alternative Medicine Review Volume 14, Number 4 2009

Over 150 chemicals have been shown to cause a reduction in TSH and/or thyroid hormone. Heavy metals such as lead and cadmium disrupt thyroid function

Howdeshell KL. A model of the development of the brain as a construct of the thyroid system. Environ Health Perspect. 2002 Jun;110 Suppl 3:337-48.

Luo, J., & Hendryx, M. (2014). Relationship between blood cadmium, lead, and serum thyroid measures in US adults—the National Health and Nutrition Examination Survey (NHANES) 2007–2010. International Journal of Environmental Health Research, 24(2), 125-136.

Gluten… again?

After 1 year on a gluten-free diet:

- Understand the difference between Celiac, NCGS, and modern hybridized wheat reactions
- Subclinical hypothyroidism normalized in 71% patients with non-autoimmune disease
- 60% of patients with autoimmune thyroid disease resolved to euthyroidism
- 80% subjects with no improvement in thyroid function, compliance with the diet was poor

Sategna-Guidetti C, et al. (2001). Prevalence of thyroid disorders in untreated adult celiac disease patients and effect of gluten withdrawal: an Italian multicenter study. Am J Gastroenterol, 2001 Mar;96(3):751-7.

Thyroid testing controversy

Most primary care physicians have been trained to test only the thyroid stimulating hormone (TSH.) The accepted range for normal has changed, though many labs have not updated the reference range. Still, there is a disagreement as to what constitutes 'normal.'

- National Academy of Clinical Biochem-istry (NACB) 0.4-2.5 uIU/ml
- American College of Clinical Endocrinologists (ACCE) 0.3–3.04 uIU/ml
- European Thyroid Association (ETA) 0.4-2.5 uIU/ml

Testing TSH only may not give an accurate indication of the T_3 delivered to the thyroid receptor.

Thyroid testing controversy

There is a wide variety of opinion on the internet about the best approach to testing. The free T3 and free T4 now give accurate representations of free hormone levels. To understand hormone production, conversion, and delivery, the following tests may be helpful:

- TSH, free T3, free T4, reverse T3, total T3, anti-thyroid antibodies (TPOAb &TGAb,) morning urine SPOT iodine
- This accounts for free hormones, analyzing hormone ratios, and ruling out developing autoimmune disease
- Ratios: freeT3/ freeT4 >0.33 and total t3/reverse T3 >6
- This panel is not needed at every lab draw, and is based on clinical presentation

Reverse T_3 effects

- RT_3 can effectively block enzymatic conversion of T_4-T_3 and can block T_3 from binding the thyroid receptor
- Consequences:
  - May be adaptive in disease, starvation, and stress situations to slow metabolism
  - Our modern lifestyle and environment can trigger this adaptive response
  - High RT_3 levels with potentially normal T_3, may still feel 'hypo' due to receptor blockade
  - Or… T_4 may be available but excessively converting to RT_3, resulting in low T_3 and 'hypo' symptoms with normal TSH and T_4 levels
  - Potatoe story and epigenetics

In summary, an adaptive RT_3 response can cause hypothyroid symptoms- even with "normal" thyroid levels.

Factors that Affect Thyroid Function

T4

Factors that contribute to proper production of thyroid hormones

- Nutrients: iron, iodine, tyrosine, zinc, selenium vitamin E, B2, B3, B6, C, D

Factors that inhibit proper production of thyroid hormones

- Stress
- Infection, trauma, radiation, medications
- Fluoride (antagonist to iodine)
- Toxins: pesticides, mercury, cadmium, lead
- Autoimmune disease: Celiac

Factors that increase conversion of T4 to RT3

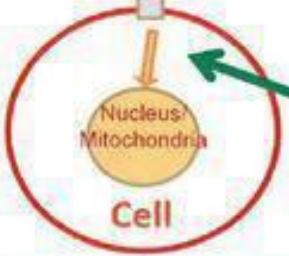
- Stress
- Trauma
- Low-calorie diet
- Inflammation (cytokines, etc.)
- Toxins
- Infections
- Liver/kidney dysfunction
- Certain medications

Factors that increase conversion of T4 to T3

- Selenium
- Zinc

RT3 T3

T3 and RT3 compete for binding sites



Factors that improve cellular sensitivity to thyroid hormones

- Vitamin A
- Exercise
- Zinc

Lifestyle as treatment and prevention

- Our moment to moment everyday choices are our most powerful medicine
- Components of Lifestyle Medicine:
  - Nutrition
  - Fitness
  - Stress Management
  - Healthy Relationships

- Synergistic effects:
  - Inflammation/Immune Balance
  - Positive genetic Expression
  - Lowered blood pressure
  - Hormonal Balance
  - Heart disease reversal
  - And more…

Nutrients to Consider in Thyroid Health

- Zinc (15-30 mg)
  - Cofactor at thyroid hormone receptor
- Selenium (200-400 mcg)
  - Essential part of Deiodinases, Glutathione peroxidase, Selenoprotein P, & Thioredoxin
- Iron (aim for ferritin of 60-100)
  - Thyroperoxidase (TPO) is heme dependent
- Iodine (150-200 mcg)
  - 9% omnivores, 25% of vegetarians, 80% of vegans have low iodine (<100 µg/l urine iodine)
  - Narrow therapeutic window. Dosage for thyroid is in MCG not MG.
- Vitamin A (2000 iu)
  - Retinoic acid plays a role in thyroid hormone nuclear signalling
- Vitamin D (2000 iu or to serum D3 level of 60-80 in AIT)
  - Immune regulatory effects help prevent and/or moderate Autoimmune thyroid disease (AIT)

Thyroid Treatments

Thyroid medications can group into the following categories:

- T4 (Levothyroxine, Synthroid, Levoxyl)
- T4/T3 (4:1 or 3:1 ratio Compounded, Thyrolar, Liotrix)
- T3 (Liothyronine, Triiodothyronine, Cytomel, Compounded SR T3)
- Natural Dessicated Thyroid (Armor, Naturethroid, WPThyroid, Westhroid)
- OTC Glandulars (Desiccated porcine, ? pharmaceutical standards)

As you have seen, there might not be a 'one size fits all' solution. If an individual has difficulty in their T4 production but has good T4->T3 conversion, then T4 may be appropriate. If T4->T3 conversion is impaired despite addressing underlying causes, then a combination T4/T3 preparation may be more appropriate.

‘Truth is a relationship. Life is synergetic.’ R. Buckminster Fuller

Thanks! And any questions?