FUNCTIONAL MEDICINE
Continuing Education

Hypothyroidism & Women's Wellness

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Disclosures

- Lara Zakaria does not report any actual or potential conflicts of interest in relation to this continuing pharmacy education course.

Objectives

1. Discuss pathophysiology of thyroid disorders
2. Review evaluation of hypothyroid conditions.
3. Recommend treatment plans for hypothyroid patients that include dietary changes, gut healing, and nutrient supplementation.

Meet Amanda

- “Exhausted all the time”
- Trouble concentrating
- OTC stool softener (constipation)
- Her partner and her have been trying to conceive for almost a year

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Prevalence and Impact of Thyroid Disease

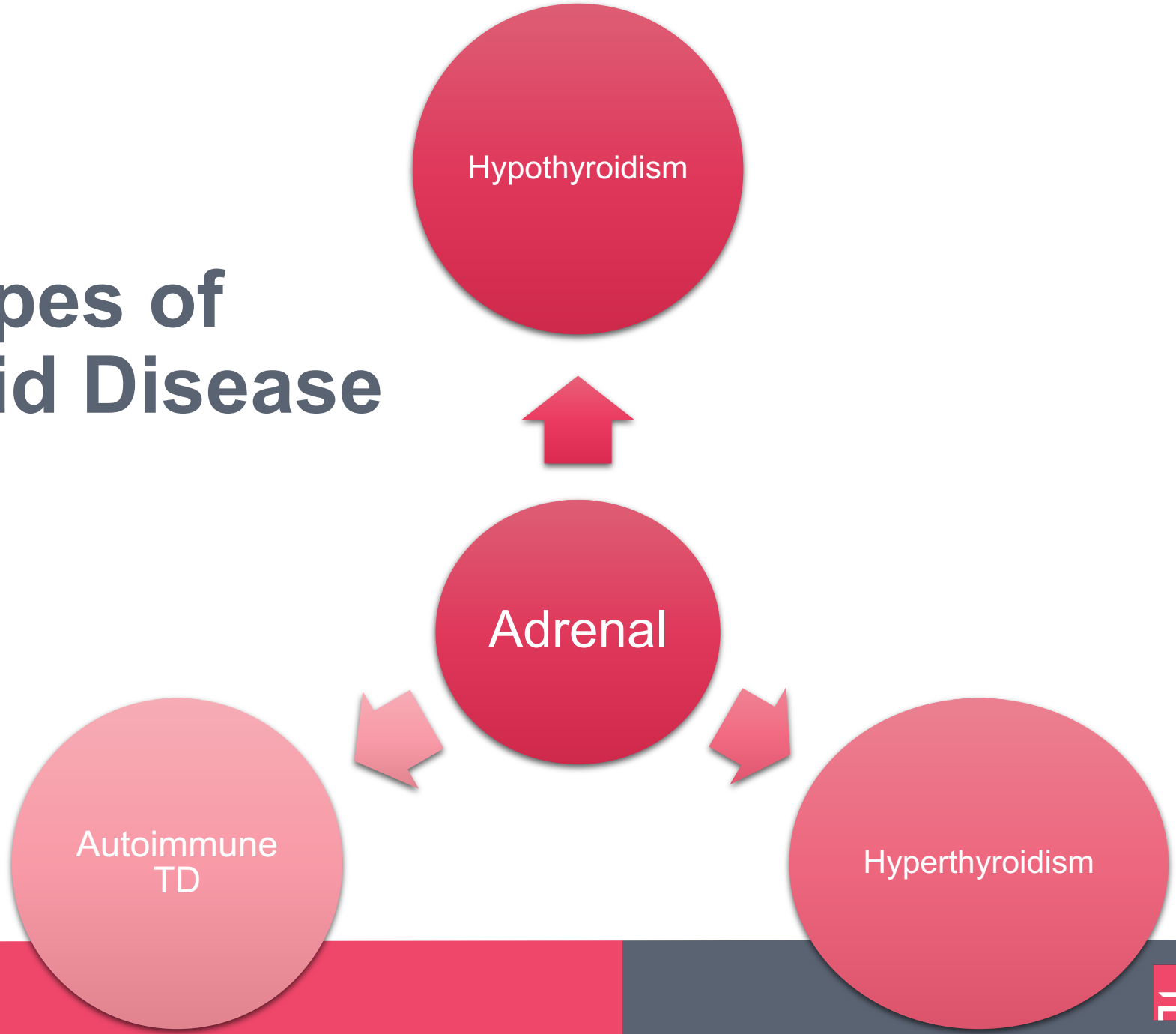
- 12% + of the population will develop a thyroid condition during their lifetime (United States)
- An estimated 20 million Americans have some form of thyroid disease (TD)
- Up to 60% of those with TD are unaware/undiagnosed
- Thyroid conditions are 5-8x more common in women than men
- 1 in 8 women will develop a thyroid disorder during her lifetime
- Undiagnosed/untreated TD increases risk of cardiovascular diseases, osteoporosis, and infertility

American Thyroid Association, https://www.thyroid.org/

Pathophysiology of Thyroid Disease

Hypothyroidism, Hyperthyroidism, and Autoimmune

Subtypes of Thyroid Disease



Hypothyroidism

- Inadequate production of thyroid hormone
- Inadequate activation of thyroid hormone
- Primary hypothyroidism
- Autoimmune hypothyroidism
- Hypofunction secondary to nutrient depletions, adrenal fatigue

Hypothyroidism signs and symptoms include:

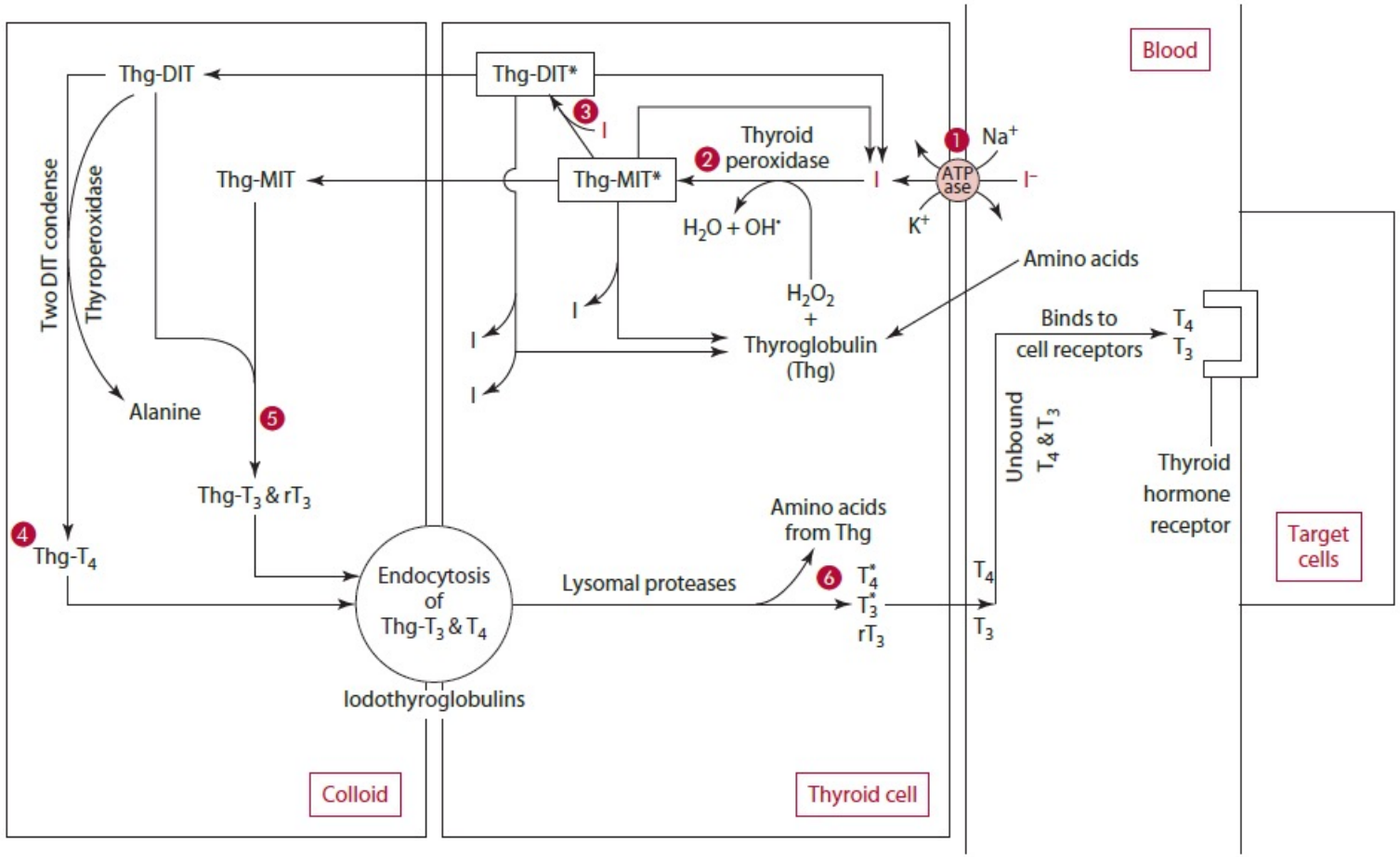
Fatigue	Increased sensitivity to cold	Constipation	Dry skin	Weight gain	Puffy face
Hoarseness	Muscle weakness	Elevated blood cholesterol (LDL)	Muscle aches, tenderness and stiffness	Joint pain, stiffness or swelling	Heavy or irregular menstrual periods
Thinning hair	Slowed heart rate	Depression	Impaired memory/brain fog	Enlarged thyroid gland (goiter)	

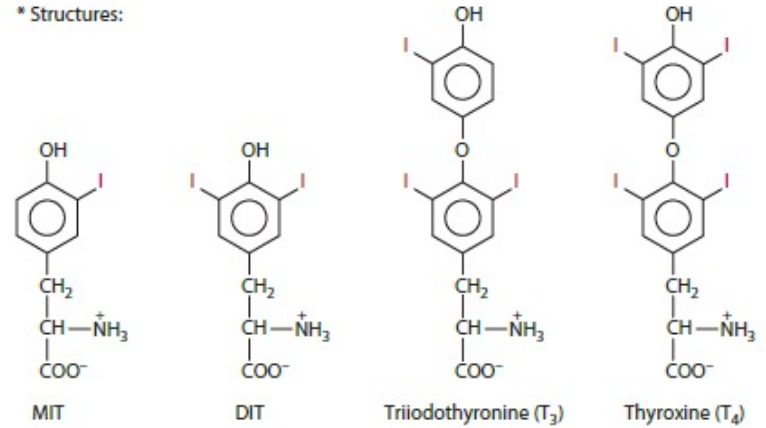
The Mayo Clinic. Hypothyroidism (underactive thyroid). https://www.mayoclinic.org/diseases-conditions/hypothyroidism/
PLoS One. 2019;14(7):e0219769

Hypothyroidism complications when left untreated

- Goiter (enlargement of thyroid)
- Increased risk of heart disease, including heart failure
- Mental health issues, including depression and brain fog
- Peripheral neuropathy
- Myxedema (intense cold intolerance and drowsiness, followed by profound lethargy)
- Infertility, irregular ovulation
- Miscarriage, birth defects and developmental delays

The Mayo Clinic. Hypothyroidism (underactive thyroid). https://www.mayoclinic.org/diseases-conditions/hypothyroidism/

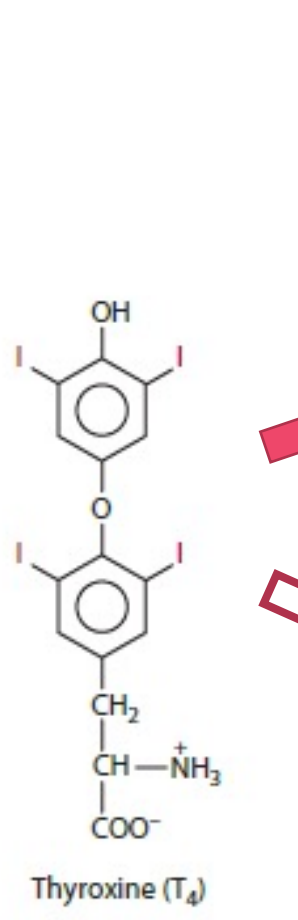




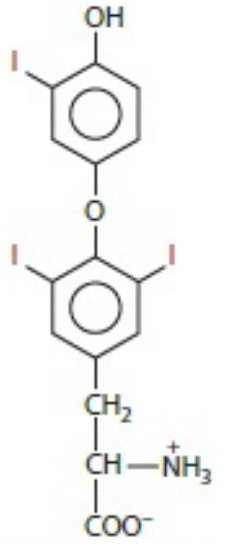
1. I^- is actively transported into the thyroid cell.
2. I is bound to a tyrosine residue on thyroglobulin to form thyroglobulin-3-monoiodotyrosine (Thg-MIT).
3. Thg-MIT is iodinated to form Thg-DIT, thyroglobulin-3, 5-diodotyrosine, which 4 condenses with another Thg-DIT in the colloid to form Thg-T_4.
5. Thg-DIT also can condense with Thg-MIT to form Thg-T_3 and reverse (r)T_3.
6. T_4 and T_3, active thyroid hormones, are released into the blood following endocytosis of Thg-T_3 and Thg-T_4 back into the thyroid cell and hydrolysis of the Thg by proteases.

Figure 13.19 Overview of iodine intrathyroidal metabolism and homogenesis

Production of T4 & Activation



Thyroxine (T_4)



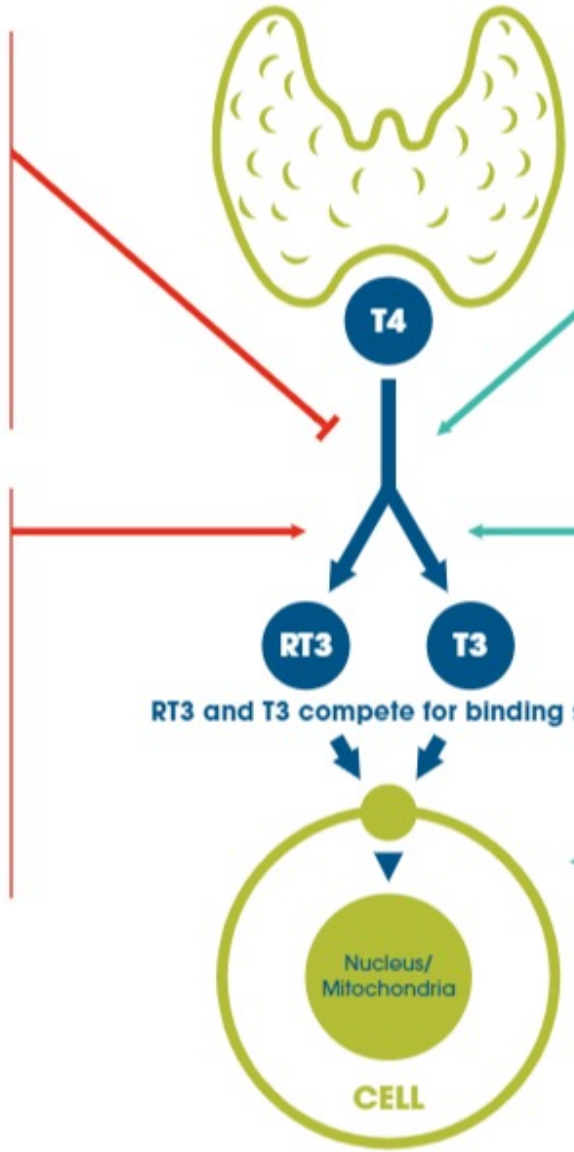
Triiodothyronine (T_3)

rT3

Cell & receptor

Gropper, SS, Smith JL, Carr TP. Advanced Nutrition and Human Metabolism. 7th edition. 2018.

Factors that Affect Thyroid Function



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 contribute to proper production of thyroid hormones

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

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

Factors that improve cellular sensitivity to thyroid hormones

- Vitamin A
- Exercise
- Zinc

Three mechanisms of thyroid hypofunction

Production

- Iron, iodine, tyrosine, selenium, Vit C, D E, and B2, B3, B6

Activation to T3

- Selenium, zinc
- Stress and adrenal support

Thyroid receptor sensitivity

- Zinc, Vit A
- Exercise

Quick Quiz

Your patient is on levothyroxine (T4) and her TSH labs seem fine. But she comes in and reports she's still feeling sluggish, "lost focus" and still seeing consistent hair loss. What is likely the problem?

- ❑ Nothing, it's in her head since her TSH is normal
- ❑ She needs a higher dose of levothyroxine
- ❑ She might need to switch to a T3/T4 combo
- ❑ She might need support in nutrients/lifestyle factors that impact T3 conversion vs T4 production

Hyperthyroidism

Pathophysiology

- Increased synthesis or release of preformed thyroid hormones, or an endogenous or exogenous source (medication)

Causes

- Most common causes of excessive thyroid hormone production are Graves disease, toxic multinodular goiter, and toxic adenoma
- Common causes of excessive passive release of thyroid hormones are silent thyroiditis

Treatment

- Antithyroid medications (methimazole and propylthiouracil)
- **Beta-blockers** (atenolol, propranolol) and **glucocorticoids** (reduce conversion of T4 to T3)
- Radioactive iodine ablation of the thyroid gland (most common treatment)
- Surgical thyroidectomy

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Am Fam Physician. 2016;93(5):363-370

Hyperthyroidism

Drug-Induced

- Amiodarone
- Interferon-alpha
- Interleukin-2
- Lithium-induced thyroiditis

Hormone-replacement Tx

- Excess dose T4 or T3

Table 1. Etiology and Pathogenesis of Hyperthyroidism

Etiology	*Mechanism*
Most common causes	
Graves disease	Autoimmune process in which antibodies stimulate the TSH receptor leading to overproduction of thyroid hormones
Painless or transient (silent) thyroiditis	Autoimmune destruction of thyroid tissue leading to a release of preformed thyroid hormones
Toxic adenoma (Plummer disease)	Somatic mutation in TSH receptor or Gs alpha gene in a thyroid nodule
Toxic multinodular goiter	Expansion of clonogenic cells with an activating TSH receptor mutation
Less common causes	
Drug-induced thyroiditis	Overproduction of thyroid hormones (amiodarone-induced thyrotoxicosis type 1) or release of preformed thyroid hormones (amiodarone-induced thyrotoxicosis type 2, interferon alfa, interleukin-2, or lithium)
Hyperemesis gravidarum	High level of β-hCG stimulates TSH receptors
Postpartum thyroiditis	Variant of painless thyroiditis with the same mechanism, occurring after delivery
Subacute granulomatous (de Quervain) thyroiditis	Painful inflammation of the thyroid gland caused by viral infection, often with fever, triggering a release of preformed thyroid hormones
Rare causes	
Factitious thyrotoxicosis	Surreptitious ingestion of thyroid hormones
Metastatic follicular thyroid cancer	Metastasis of functional follicular thyroid cancer
Struma ovarii	Ectopic thyroid tissue in ovarian dermoid tumor produces thyroid hormones
Trophoblastic tumor or a germ cell tumor	Tumor produces β-hCG, which stimulates thyroid TSH receptors
TSH-secreting pituitary adenoma	Tumor secreting large quantities of TSH, and not responding to thyroxine and triiodothyronine feedback

β-hCG = beta human chorionic gonadotropin; TSH = thyroid-stimulating hormone.

Information from references 1 through 9.

Am Fam Physician. 2016;93(5):363-370

Hyperthyroidism

Signs

- Irregular pulse, tachycardia, A. fib
- Fever (thyroid storm)

Symptoms

- Palpitations
- Anxiety, insomnia
- Tremor
- Heat intolerance
- Hyperpigmentation (face and neck)
- Weight loss (difficulty gaining weight)

Table 2. Signs and Symptoms of Hyperthyroidism

Adrenergic

Palpitations, tachycardia, anxiety, tremor, jitteriness, diaphoresis, heat intolerance, stare, lid lag, hyperdefecation (not diarrhea)

Cardiovascular

Tachycardia, irregular pulse (in atrial fibrillation), dyspnea, orthopnea and peripheral edema (in heart failure)

Cutaneous

Onycholysis (Plummer nails), patchy or generalized hyperpigmentation (especially of the face and neck)

Symptoms pathognomonic for Graves disease: pretibial myxedema (thyroid dermopathy) and thyroid acropachy (clubbing of fingers and toes accompanied by soft-tissue swelling of the hands and feet)

Patchy vitiligo can also be observed in Graves disease

Hypermetabolism

Weight loss in spite of increased appetite, fever (in thyroid storm)

Neuromuscular

Brisk peripheral reflexes with accelerated relaxation phase and weakness of proximal muscles

Neuropsychiatric

Anxiety, rapid and pressured speech, insomnia, psychosis (if hyperthyroidism is severe)

Ocular

Increased lacrimation, incomplete closure of the eyes when sleeping reported by the patient's partner, photophobia, increased eye sensitivity to wind or smoke, grittiness or sensation of a foreign body or sand in the eyes

Symptoms pathognomonic for Graves disease: exophthalmos, periorbital edema, diplopia, blurred vision, reduced color perception

Information from references 10 through 18.

Am Fam Physician. 2016;93(5):363-370

Autoimmune Thyroid Disease (AITD)

- T-cell mediated dysregulation of the immune system leading to immune attack of the thyroid
- Prevalence of AITD is estimated to be ~ 5%; however, due to challenges in diagnosis, the prevalence of antithyroid antibodies may be even higher (undiagnosed AITD)
- Two main clinical presentations: Graves' disease (GD) manifesting as thyrotoxicosis and Hashimoto's thyroiditis (HT) mainly manifesting as hypothyroidism
- Hoshimoto's is the #1 cause of thyroid disease in the country
- Disproportionately impacts women, and risk is increased in the presence of other autoimmune disease(s)
- Distinguished from non-AITD by assessing antibodies in addition to thyroid function labs

Autoimmun Rev. 2015;14(2):174-180

Th1 induced cytokine production

The prevalence of 90% for AbTPO

Prevalence of AbTg is 25–50%

In young patients with thyroiditis, however, AbTg may be present in the absence of AbTPO

AbTg are not thought to be pathogenic because they are predominantly IgG1 and 4 (alternative mechanism?)

Therefore, AbTPO are a sensitive marker of AITD in both thyroiditis and GD and is often present in subclinical hypothyroidism.

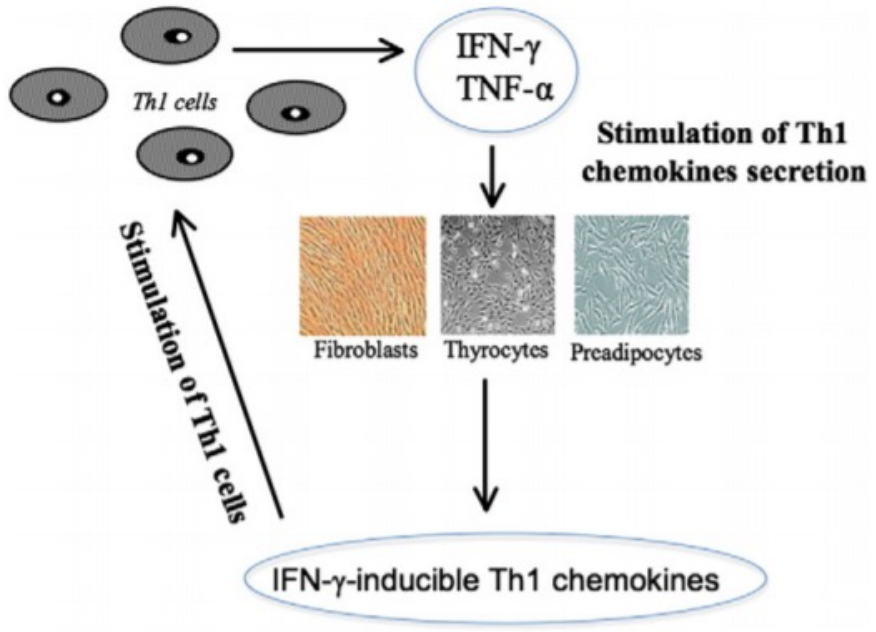

Fig. 1. In thyroid (and orbital tissue of GO patients), recruited Th1 lymphocytes may be responsible for enhanced IFN-γ and TNF-α production, which in turn stimulates CXCL10 (the prototype of the IFN-γ-inducible Th1 chemokines) secretion from the cells, therefore creating an amplification feedback loop, that initiates and perpetuates the autoimmune process.

Autoimmun Rev. 2015;14(2):174-180

Triggers for AITD

- Genetics (multiple factors)
- Environmental factors including radiation, exposure to halides, smoking
- Food triggers, including gluten and other food sensitivities
- Nutrient depletion/imbalance (especially iodine, selenium, but many others)
- Pathogens, especially viruses
- Dysbiosis & intestinal permeability (IP)
- Medications (direct include lithium, amiodarone; indirect include PPIs, antibiotics, steroids, beta blockers)
- Female sex (estrogen)
- Stress and adrenal dysfunction

Thyroid. 2010;20(7):715-725
Autoimmun Rev. 2015;14(2):174-180
Nutrients. 2020;12(6):1769
Rev Endocr Metab Disord. 2018;19(4):293-300

Treatment of Hoshimoto's (ATA)

Patients with elevated TPO antibodies but normal thyroid function tests (TSH and Free T4) do not require treatment. Patient with only a slightly elevated TSH (mild hypothyroidism) may not require medication and should have repeat testing after 3-6 months if this has not already been done. For patients with overt hypothyroidism (elevated TSH and low thyroid hormone levels) treatment consists of thyroid hormone replacement [levothyroxine]

AMERICAN THYROID ASSOCIATION
Optimal Thyroid Health for All

https://www.thyroid.org/hashimotos-thyroiditis/

Autoimmunity from a FxMed Perspective

SY*STEM'S* BASED APPROACH

UPSTREAM MEDICINE

VS

"SY*MPTOM*-BASED" APPROACH

DOWNSTREAM MEDICINE

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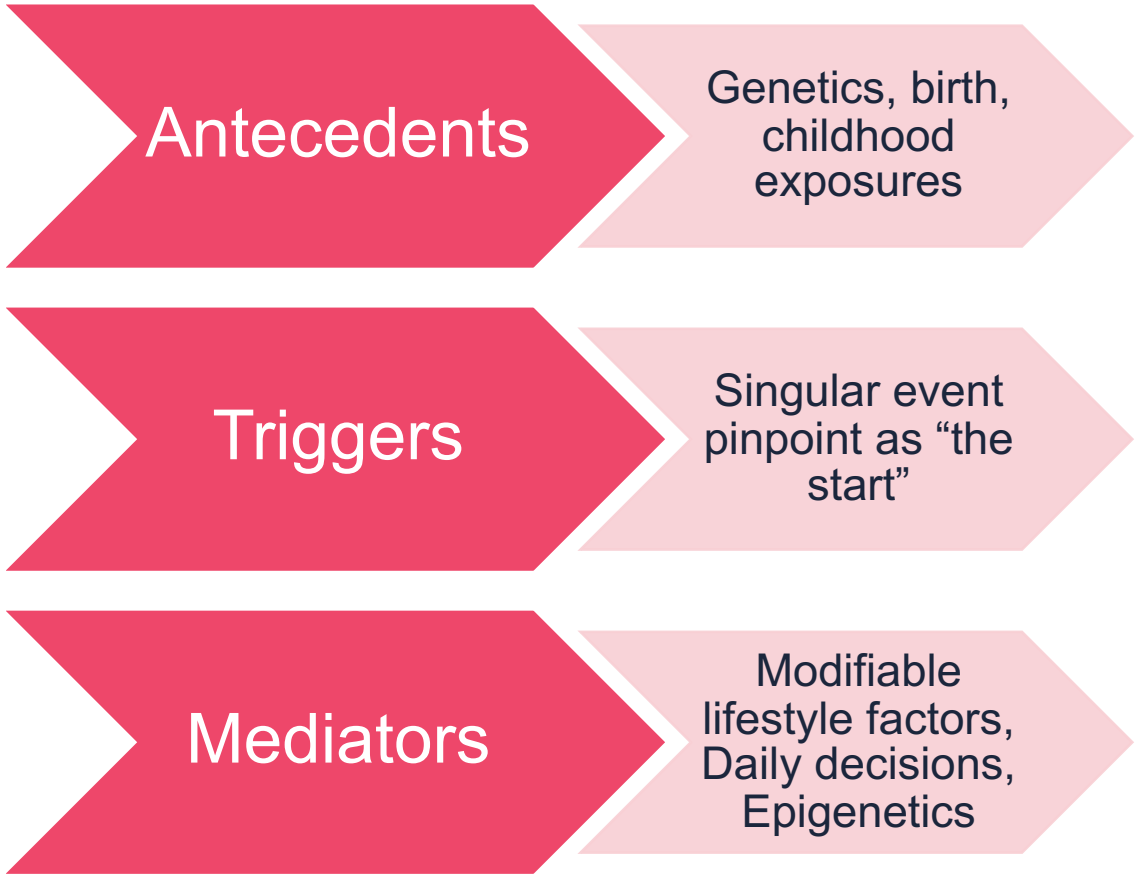
The *ATMs*


Antecedents
Genetics, birth, childhood exposures
Triggers
Singular event pinpoint as “the start”
Mediators
Modifiable lifestyle factors, Daily decisions, Epigenetics

Quick Quiz

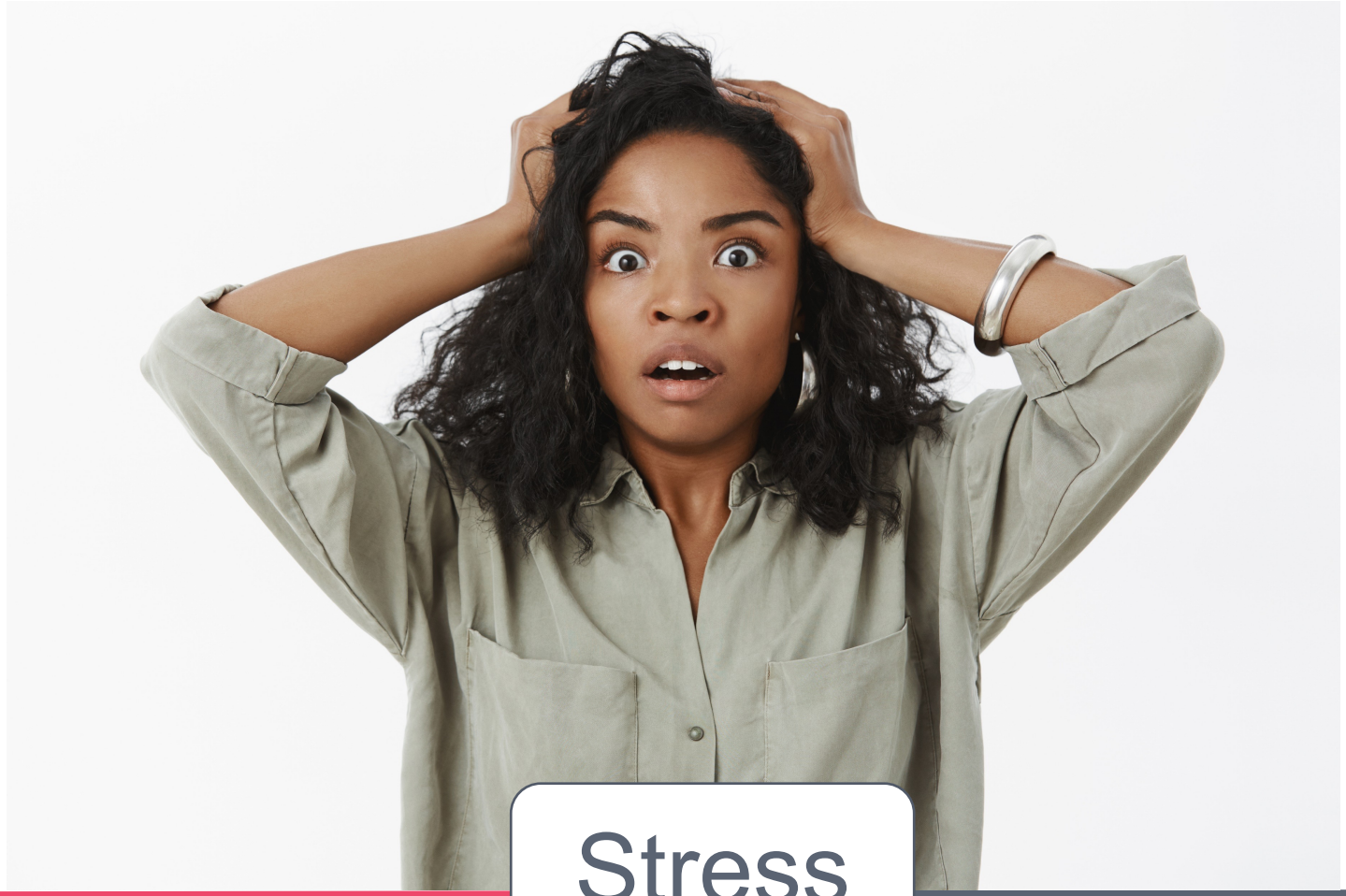
Your patient has been experiencing classic symptoms of hyperthyroidism. What laboratory changes would you expect?

- ❑ High TSH
- ❑ Low TSH
- ❑ High rT3
- ❑ High T4
- ❑ Elevated thyroid antibodies

Adrenals & Thyroid

A Tale of friendship …

What's the main underlying factor?



Adrenal stress impact on thyroid health

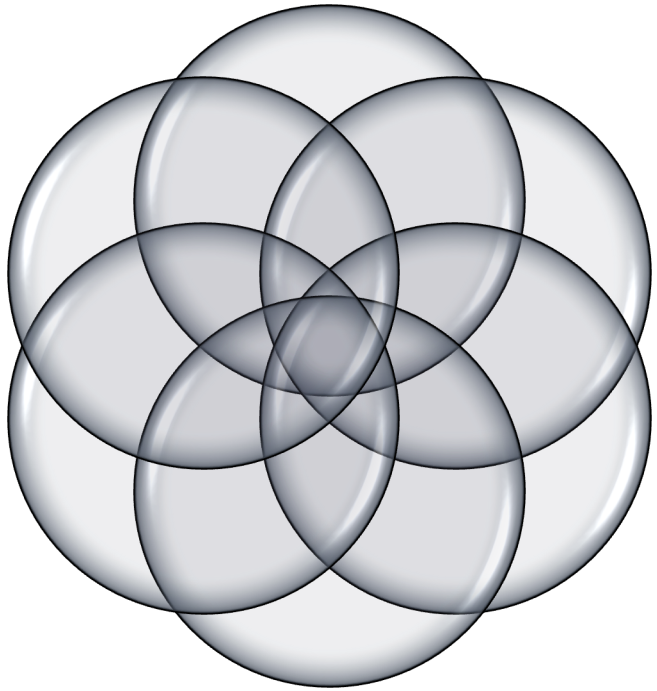
Stress response

Adrenal function, a review

Stress can look like

Emotional response

Inadequate self-care, sleep, or rest/recovery



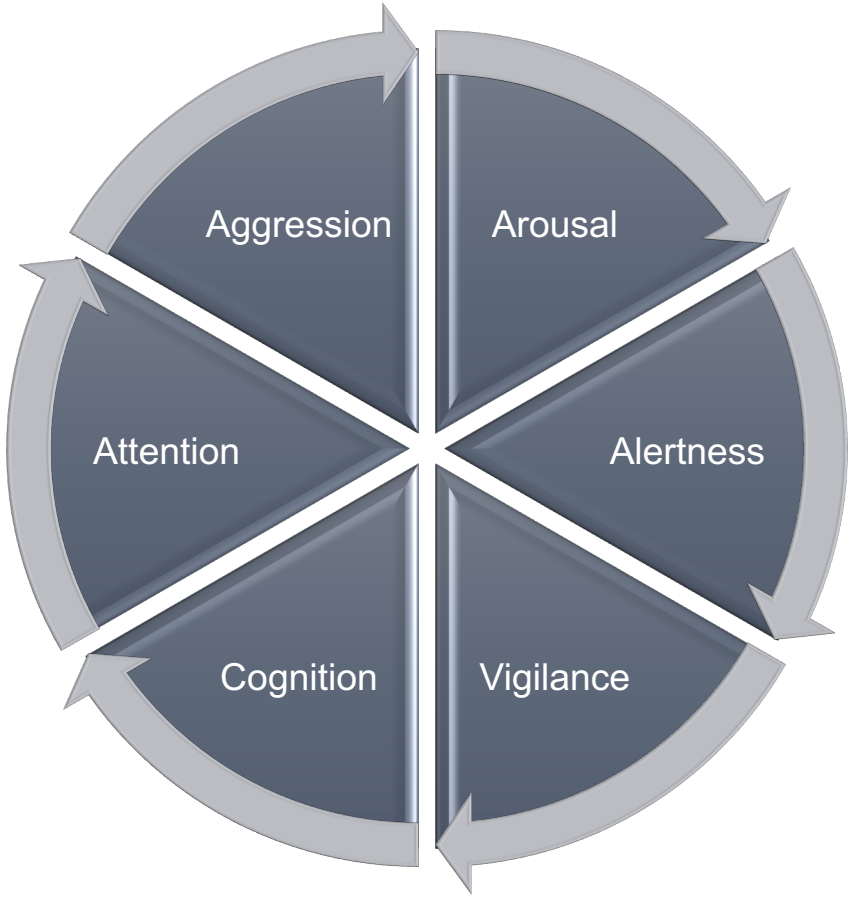
Life demands

Chronic disease/illness

Family or cultural pressures

Financial pressures

The Stress Response = “Fight or Flight”



Can stress have a positive effect?

Balance

Sympathetic

"Fight or flight"

Active, vigilant

Energy burning

Parasympathetic

"Rest or digest"

Digestion, nutrient absorption, sleep & restore

Cell repair

Sympathetic vs Parasympathetic: The Switch

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Introducing Cortisol

- The “stress” hormone
- Made in the **adrenal gland** in response to stress
- Turns on the “fight or flight response”
- Makes us more alert, signals blood flow to the muscle (get ready to run!)
- Not meant to be elevated for a long period of time

The Stress Connection

- Digestive issues & alters the microbiome balance
  - Nutrient imbalances
  - Reduced detoxification
  - Increased oxidative stress
- Leads to hormonal imbalances starting with cortisol
  - Thyroid hormone
  - Sex hormones including estrogen, testosterone, progesterone
  - Blood sugar balancing insulin

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Remember Amanda?

- 38-years-old
- Trouble concentrating, low energy, Hx of constipation, fertility challenges
- History of migraines, uses triptans and NSAIDS to manage them

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Back to Amanda

What do you think might be going on to explain her symptoms?

- Chronic exhaustion
- Trouble concentrating
- Constipation
- Infertility

Type your answers into the chat box

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Back to Amanda

You are chatting with Amanda, what questions might you ask her?

She mentions her doctor did run a thyroid test, and that her “TSH was normal”, what would you suggest as an explanation?

Type your answers into the chat box

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What her labs showed…

Test Name	In Range	Out Of Range	Reference Range	Lab
TSH	2.14		mIU/L	NL1
			Reference Range	
			> or = 20 Years 0.40-4.50	
			Pregnancy Ranges	
			First trimester 0.26-2.66	
			Second trimester 0.55-2.73	
			Third trimester 0.43-2.91	

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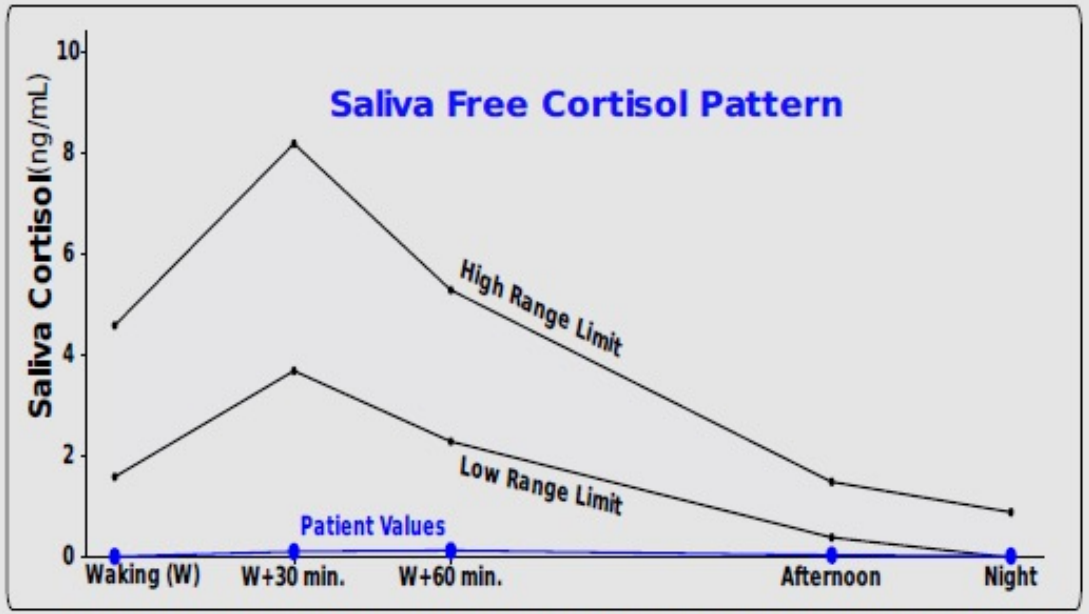
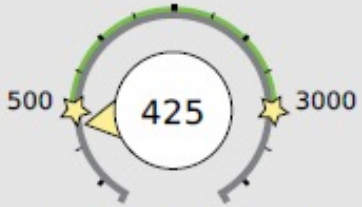
Adrenal function test gives a little more of the picture …

Adrenal Hormones See pages 4 and 5 for a more complete breakdown of adrenal hormones



Total DHEA Production

Age	Range
20-39	1300-3000
40-59	750-2000
>60	500-1200



Total DHEA Production
(DHEAS + Etiocholanolone + Androsterone)

Saliva Cortisol Total
(Sum of 5 values)

cortisol metabolism →

Metabolized Cortisol (THF+THE)
(Total Cortisol Production)

Free cortisol best reflects tissue levels. Metabolized cortisol best reflects total cortisol production.

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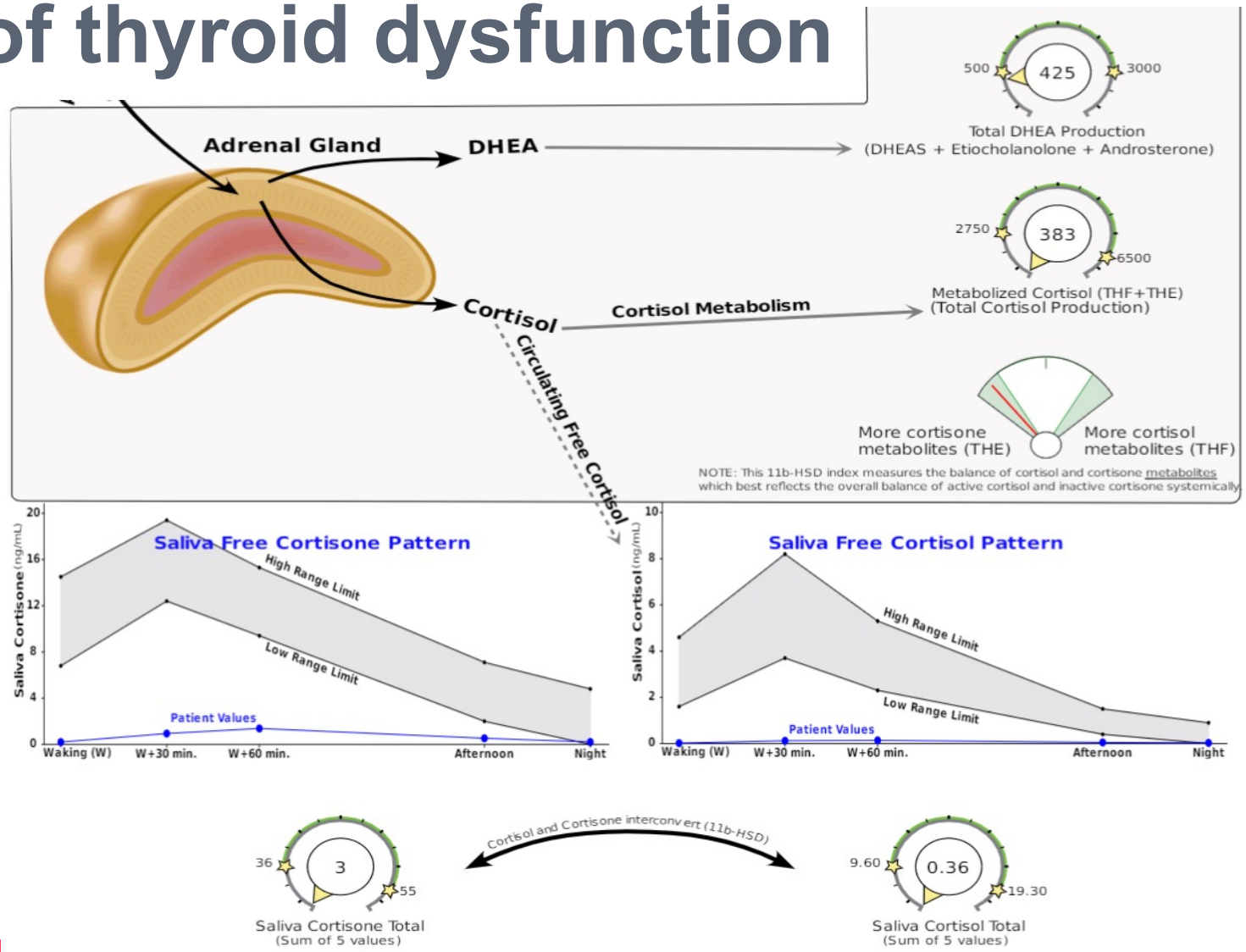
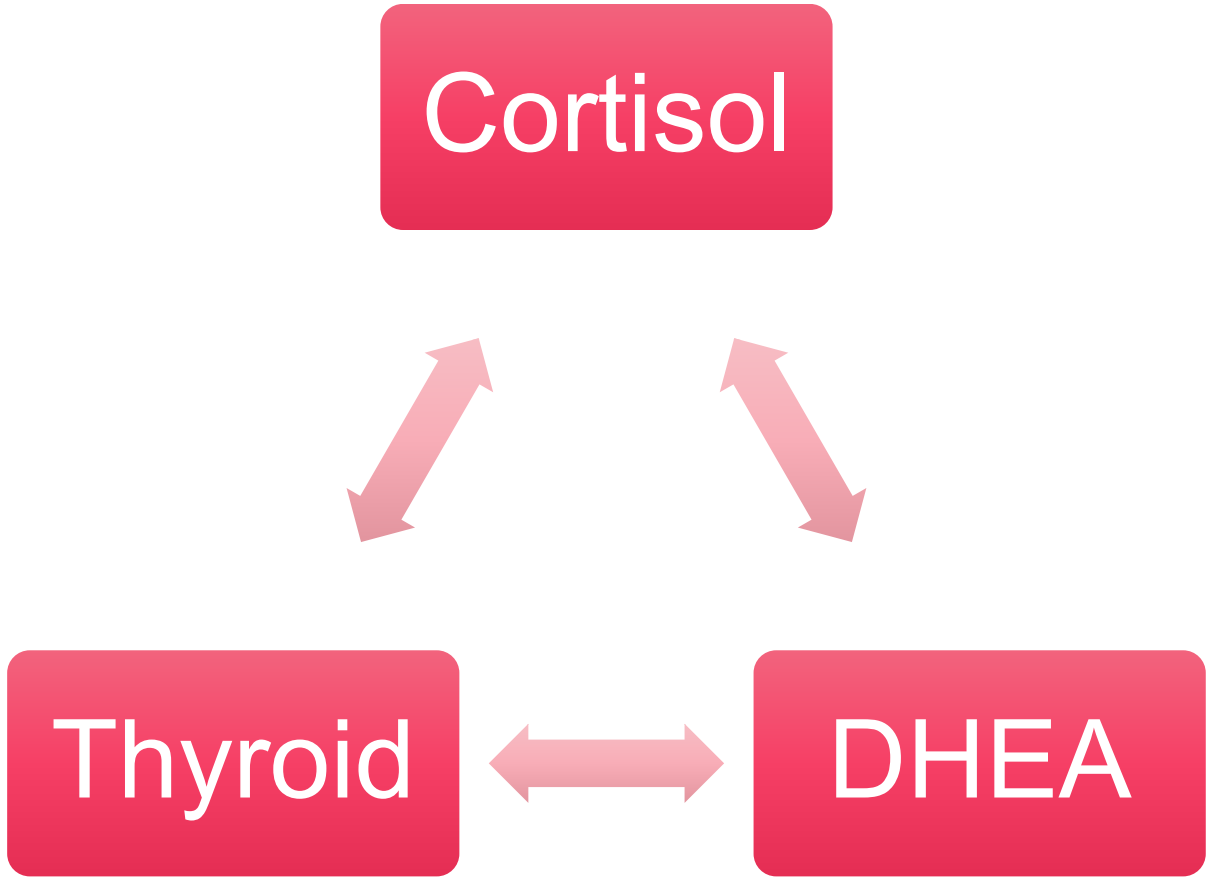
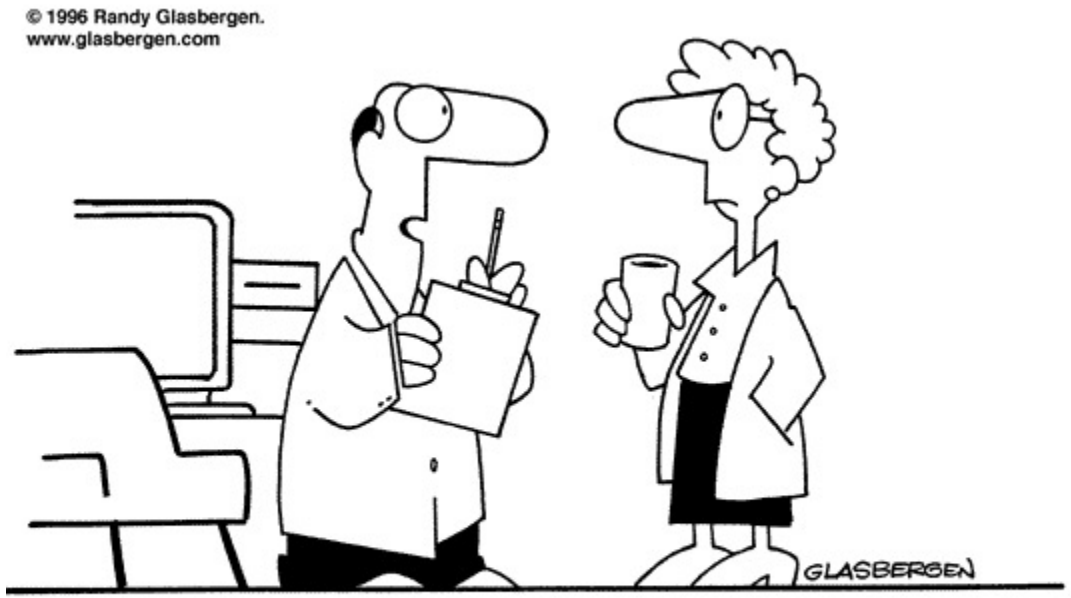
Metabolized cortisol can be an indicator of thyroid dysfunction



The Triad



Adrenals & Thyroid



"According to the latest research, the average human body is 20% water and 80% stress."

Adrenals & Thyroid

When the adrenals are stressed, it stresses out the thyroid gland

Thyroid hormones are made from an amino acid called tyrosine

- Under chronic stress tyrosine converts to excitatory neurotransmitters (epinephrine and norepinephrine)
- This leaves less tyrosine leftover to make thyroid hormone
- Combine with amino acid deficiencies, or other mineral deficiencies like (iron and others) and you end up with a significant depletion of resources for thyroid production

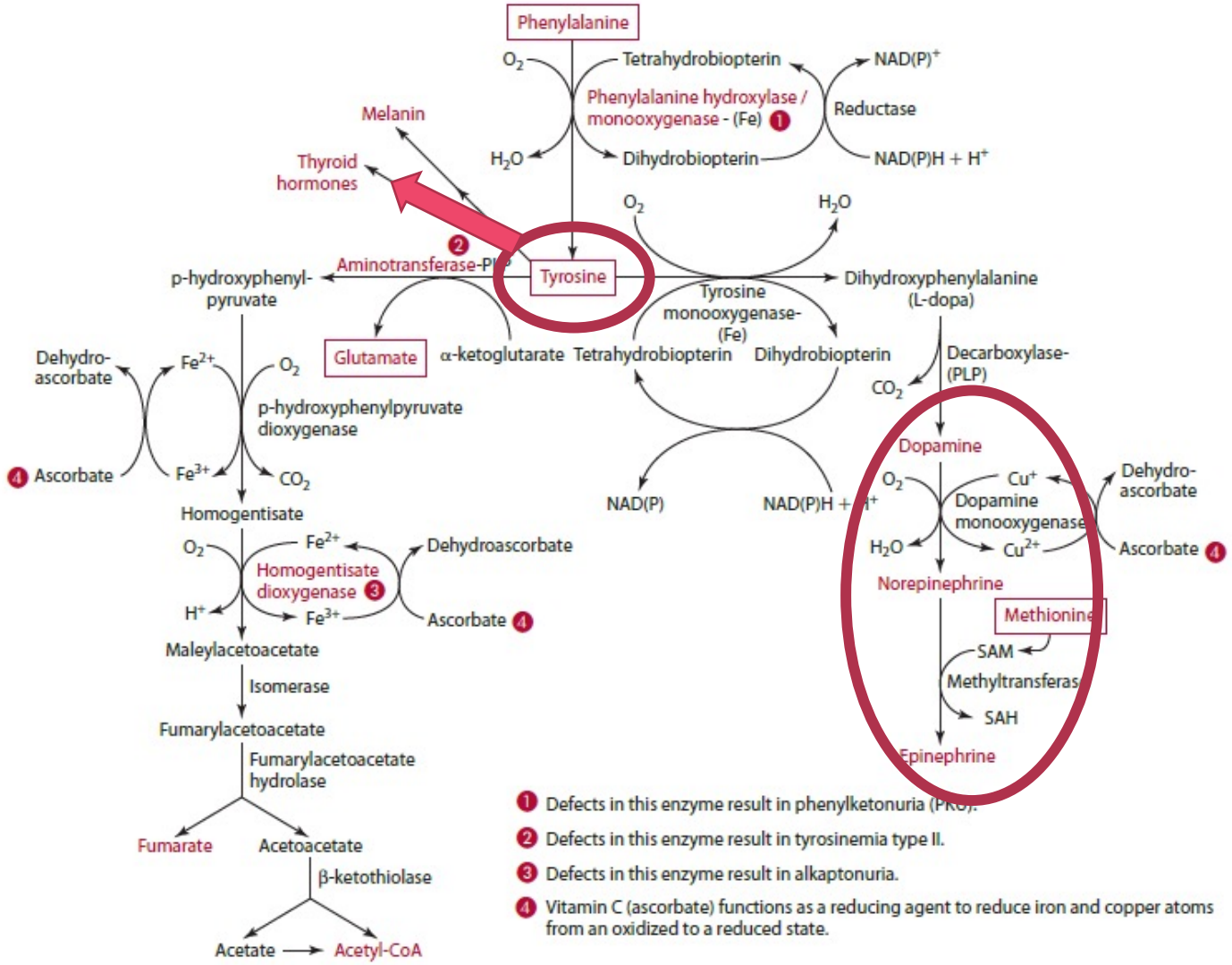


Figure 6.10 Phenylalanine and tyrosine metabolism.

Gropper, SS, Smith JL, Carr TP. Advanced Nutrition and Human Metabolism. 7th edition. 2018.

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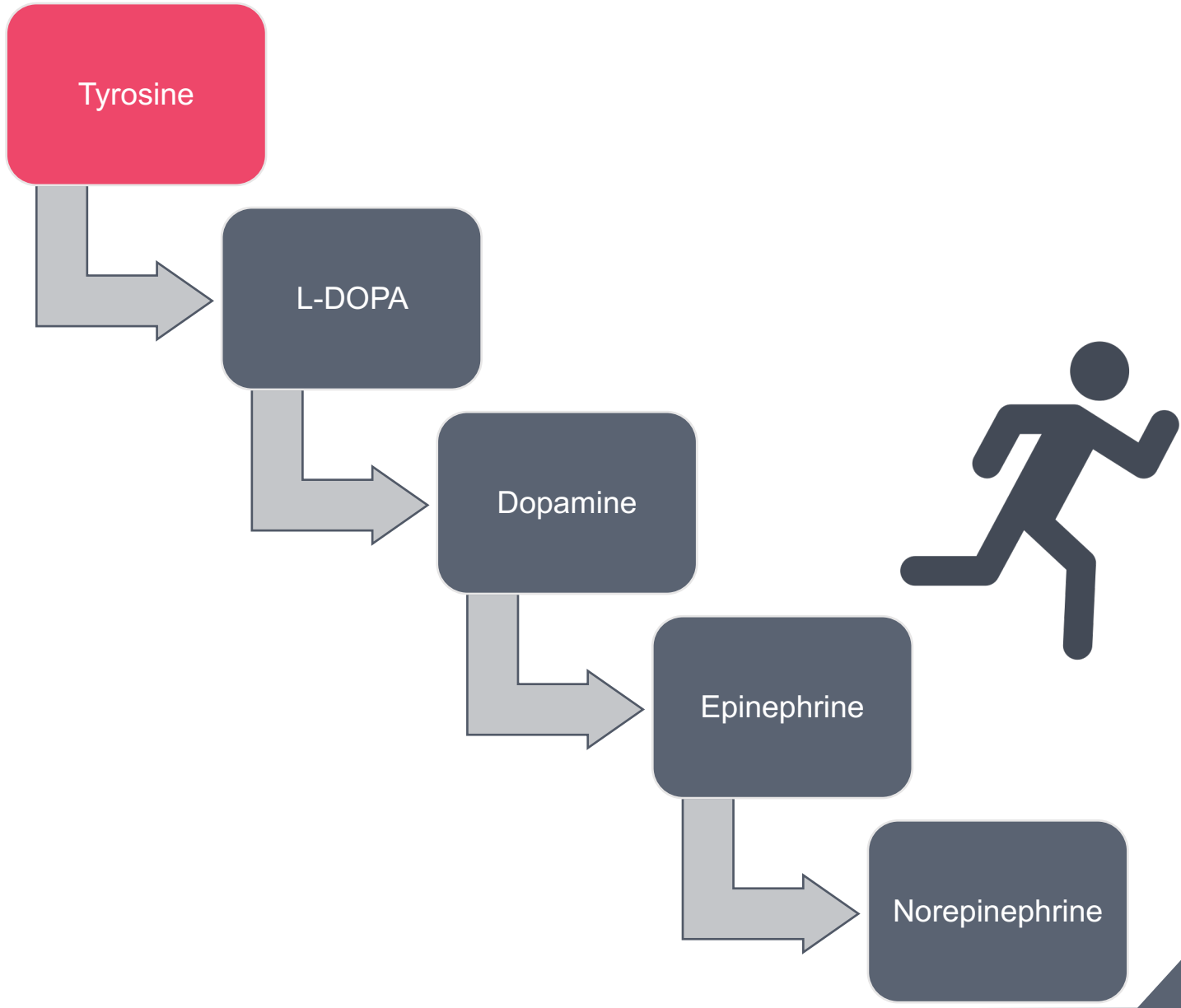
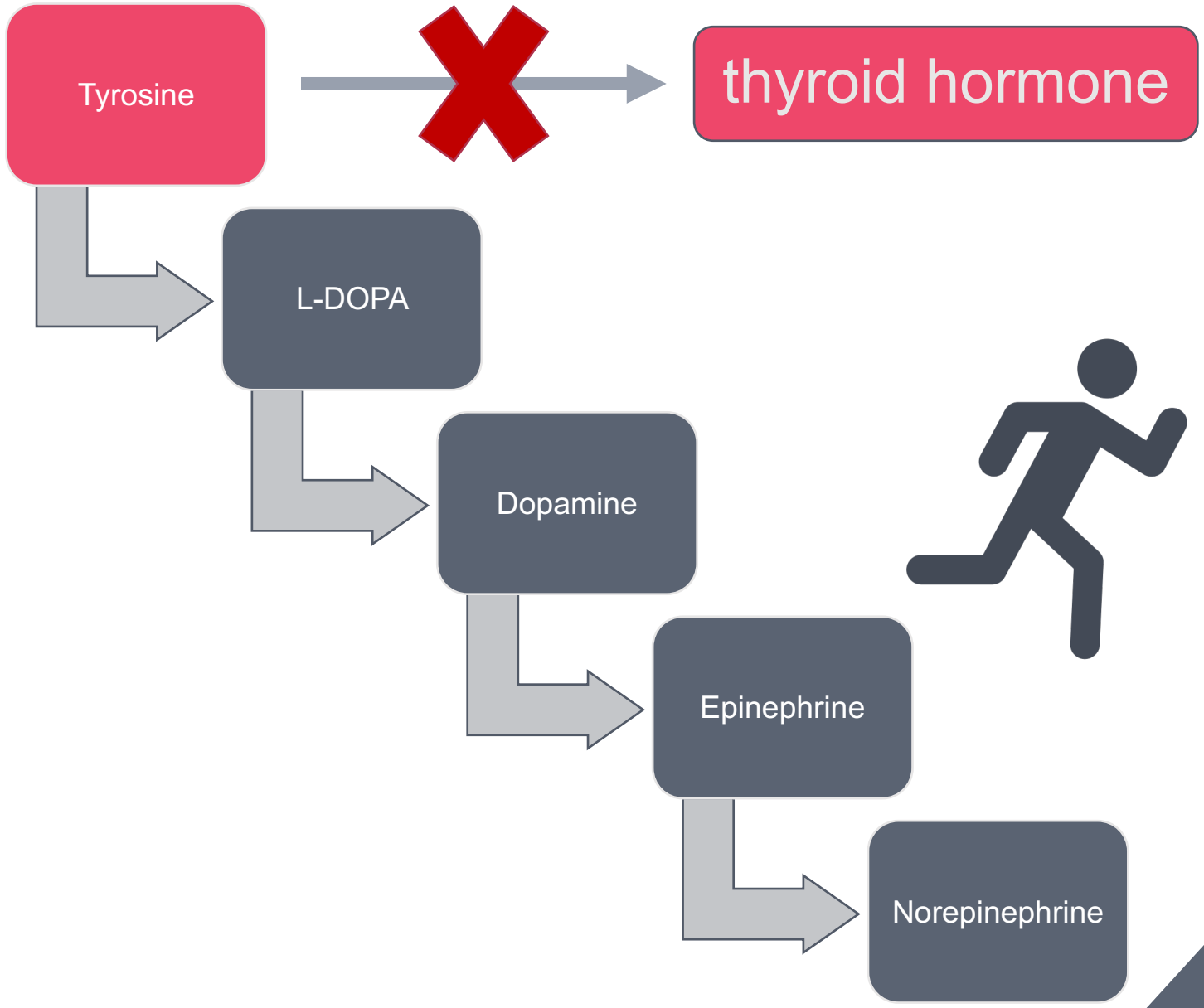
Adrenals & Thyroid



Adrenals & Thyroid



Estrogen and Thyroid Hormone Receptor Interactions: Physiological Flexibility by Molecular Specificity

NANDINI VASUDEVAN, SONOKO OGAWA, AND DONALD PFAFF

Laboratory of Neurobiology and Behavior, The Rockefeller University, New York, New York

Estrogen and Thyroid are tightly interlinked through various transcription factors, which in turn impact metabolism and fertility

Estrogen dominance increases Thyroid Binding Globulin (TBG)

Interferes with the conversion of T4 to T3

At the same time, hypothyroidism impacts estrogen detoxification through multiple mechanisms

Vasudevan, Nandini, Sonoko Ogawa, and Don
Physiological Flexibility by Molecular Specificity.

influence of thyroid hormone on estrogen actio
transfection assays, the effects of liganded thy
estrogens bound to estrogen receptors (ER) dis
isoform, *3*) the promoter through which transcrip
phenomena may be related to thyroid hormone signaling of seasonal limitations upon reproduction. The various combinations of these molecular interactions provide multiple and flexible opportunities for relations between two major hormonal systems important for neuroendocrine feedbacks and reproductive behaviors.

Physiol Rev. 2002;82(4):923-944

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Drug-Induced Nutrient Depletions (DIND)

And how they impact the thyroid

Quick Quiz

How many of you are assessing for DIND in your pharmacy practice?

- ❑ Yes
- ❑ No
- ❑ Never heard of it before

DIND: The Cycle

- Patient presents with abnormal signs or symptoms
- Medication initiated
- Medication helps with original signs/symptoms
- DIND starts to have an insidious effect
- Over weeks, months or years patient develops another set of symptoms secondary to DIND
- Patient returns to physician with new signs/symptoms
- New medication initiated
- Entire process may start all over again

Journal of Endocrinological Investigation (2020) 43:1181–1188
https://doi.org/10.1007/s40618-020-01230-8

REVIEW

Effects of oral contraceptives on thyroid function and vice versa

F. Torre[1] · A. E. Calogero[1] · R. A. Condorelli[1] · R. Cannarella[1] · A. Aversa[2] · S. La Vignera[1]

Received: 2 January 2020 / Accepted: 17 March 2020 / Published online: 26 March 2020

Abstract

Background Thyroid gland dysfunction r
ment with oral contraceptives (OCs) is fr
scanty data have been released on this ma
Aim The aim of this article was to review h
tions, interact with the hepatic production
of thyroxine (T4) and triiodothyronine (T
OCs and how they influence the thyroid f
Review The estrogenic component of the
binding protein (SHBG) and coagulation
dependent effects mainly through their a
keep the thromboembolic and cardiovascu
thyroidism or in those treated with LT4.
mean platelet volume than normal and thi
thrombocytopoietic maturation.

The estrogenic increases various liver proteins, such as TBG, sex hormone-binding protein (SHBG) and coagulation factors that impact circulating hormone.

The balance between the free and bound to protein fractions can be altered by oral contraceptives (OCs) made of estrogens and/or progestins, impacting the concentration of thyroid hormone-binding proteins

Hypothyroidism may lead to lipid alterations, systolic/diastolic pressure alterations, promoting endothelial stress and risk of deep VTE.

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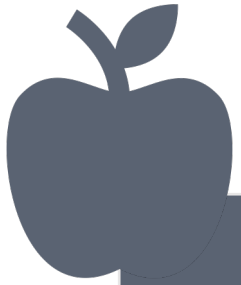
DIND for Thyroid Disease



Nutrients

- Iron
- Iodine
- Selenium
- Zinc
- Vit C
- Vit D, E
- B2, B3, B6
- Tyrosine

Medications

- Proton pump inhibitors (PPI)
- H2 blockers
- NSAIDs
- Statins
- Beta blockers (direct action on T3 activation, and nutrient depletion)
- ACEs & ARBs
- Cholestyramine
- Frequent antibiotic use
- Fluoxetine (hydrobromide)
- Glucocorticoids (direct action on T3 activation, and nutrient depletion)
- Conjugated estrogens, HRT, and OCP

TRC Natural Database. Nutrient Depletion.

Thyroid Assessment

Going beyond TSH

Thyroid Assessment

Vitals

- Abnormal temperature (consistently <98.2)
- Abnormally low/fast pulse
- Low blood pressure

Physical signs

- Hair rough, dry, breaking and/or falling out
- Skin is rough, dry, scaly, itchy
- Thinning eyebrows (especially outer portion)
- Puffy eyes, eyelids, face and/or hands/feet
- Voice more hoarse
- Eyes dry, sensitivity to light
- Irregular menstrual cycles, heavy, longer, or more frequent

Symptoms:

- Unexplained weight changes
- Cold hands/feet
- Constant exhaustion
- Brain fog
- Depression and/or anxiety; mood fluctuations
- Join/muscle pain, aches, stiffness; tendonitis, carpal tunnel, plantar fasciitis
- Low libido
- Throat hurts, pressure, difficulty swallowing

Assessment (Lab Signs)

Indirect hormone assessment

- **Thyroid stimulating hormone (TSH)**
- Consider an *early warning sign* (questionable)

Direct hormone measurement

- **Total T4 (free serum)**
- **Total T3 (free serum)**
- **Reverse T3 (rT3)**

Autoimmune panel may include:

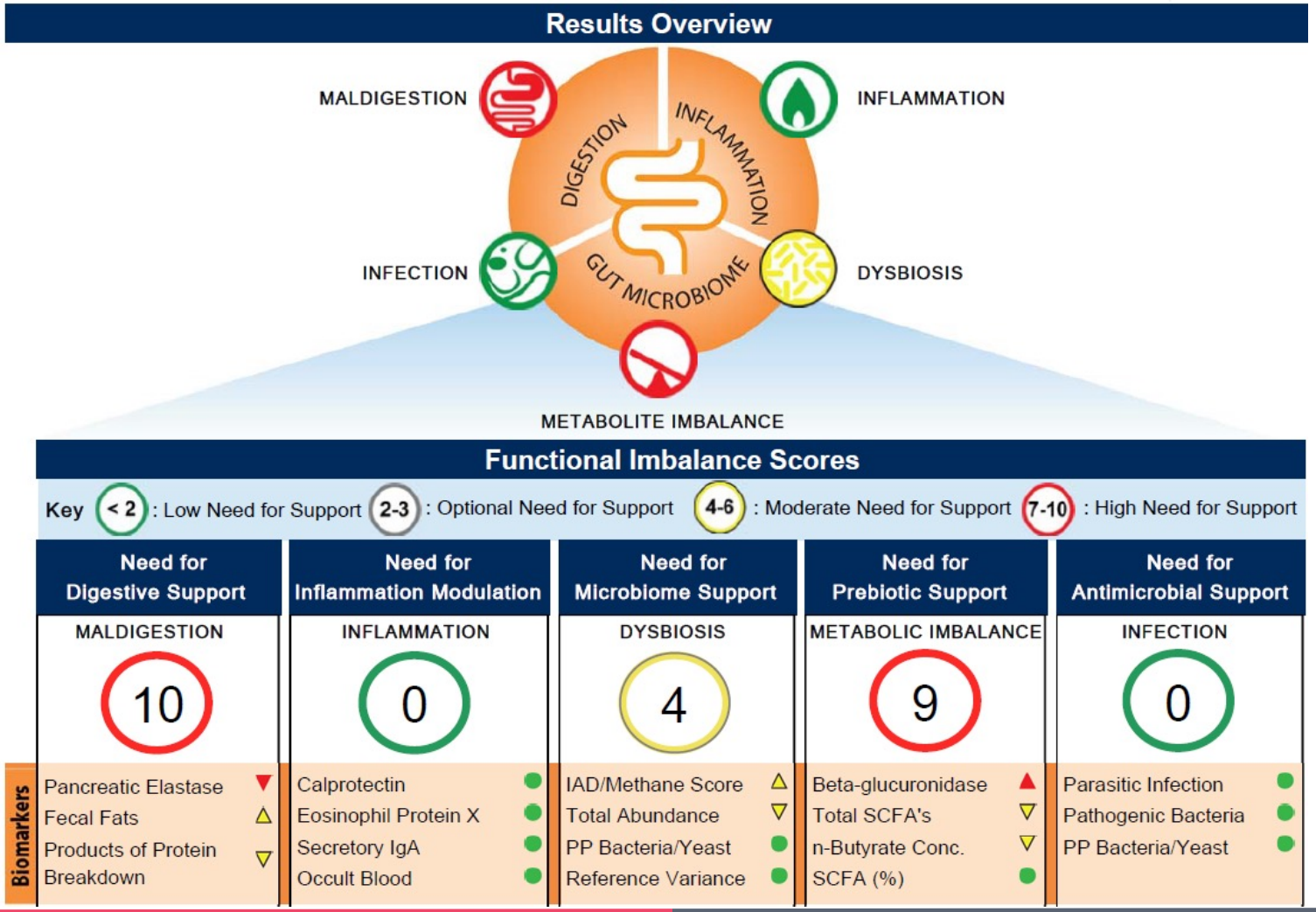
- **Thyroid Peroxidase (TPO) Antibodies (AbTPO)**
- **Thyroid Antithyroglobulin Antibody (AbTg)**
- Thyroxine-binding Globulin (TBG)
- Thyroid Stimulating Immunoglobulin (TSI)

Other considerations

- **Nutrient assessment (iron panel, zinc, selenium, vit D** and other fat-soluble vitamins, organic acids)
- GI stool test for dysbiosis, immune and digestive function
- Food sensitivity testing
- Adrenal and hormone panel (including 12- or 24-hour cortisol)

Poop

GI Function: Absorption and Inflammation



5R Protocol

Remove	Potential triggers, including polypharmacy, pathogenic organisms, food intolerances, sensitivities and allergies, or toxic exposure
Replace	Digestive aid to support improved nutrient absorption and metabolism, including digestive enzymes, or agents that promote improved motility and regular bowel movements
Reinoculate*	Provide an environment where good bacteria can thrive and where bad ones cannot
Repair	Support of the cellular repair process through the above, as well as by providing specific nutritional support for the regeneration of the GI protective barrier
Rebalance	lifestyle factors that influence the gut bacteria such as stress, sleep, exercise and relationships and assure ongoing gut health

**Arguably, reinoculated isn't as simple as "reseeding" but we use the term to simplify*

Mu Q, et al. *Front Immunol*. 2017;8:598.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5440529/

Nutrition Evaluations

Comprehensive metabolic panel (CMP)	Complete blood count (CBC)	A complete iron	Vitamin D	RBC magnesium
Selenium	Zinc	Fat soluble vitamins	Organic acids	Amino acids
	Fatty acids	Oxidative stress markers	GI function (stool testing)	

Hormone Panels

Complete thyroid panel

- TSH, total and free T4, T3, rT3
- Rule out autoimmune: Antibodies (ANA, AbTPO, AbTg)

Adrenal function

- Cortisol pattern
- Metabolized cortisol
- DHEA

Sex hormone panel

- Estrogen and metabolites
- Progesterone
- Androgens

Nutraceutical Approaches

Herbs and supplements to support optimal thyroid health

Focus on the nutrients from the 3 mechanisms of thyroid dysfunction

Production

- Iron, iodine, tyrosine, selenium, Vit C, D E, and B2, B3, B6

Activation to T3

- Selenium, zinc
- Stress and adrenal support

Thyroid receptor sensitivity

- Zinc, Vit A
- Exercise

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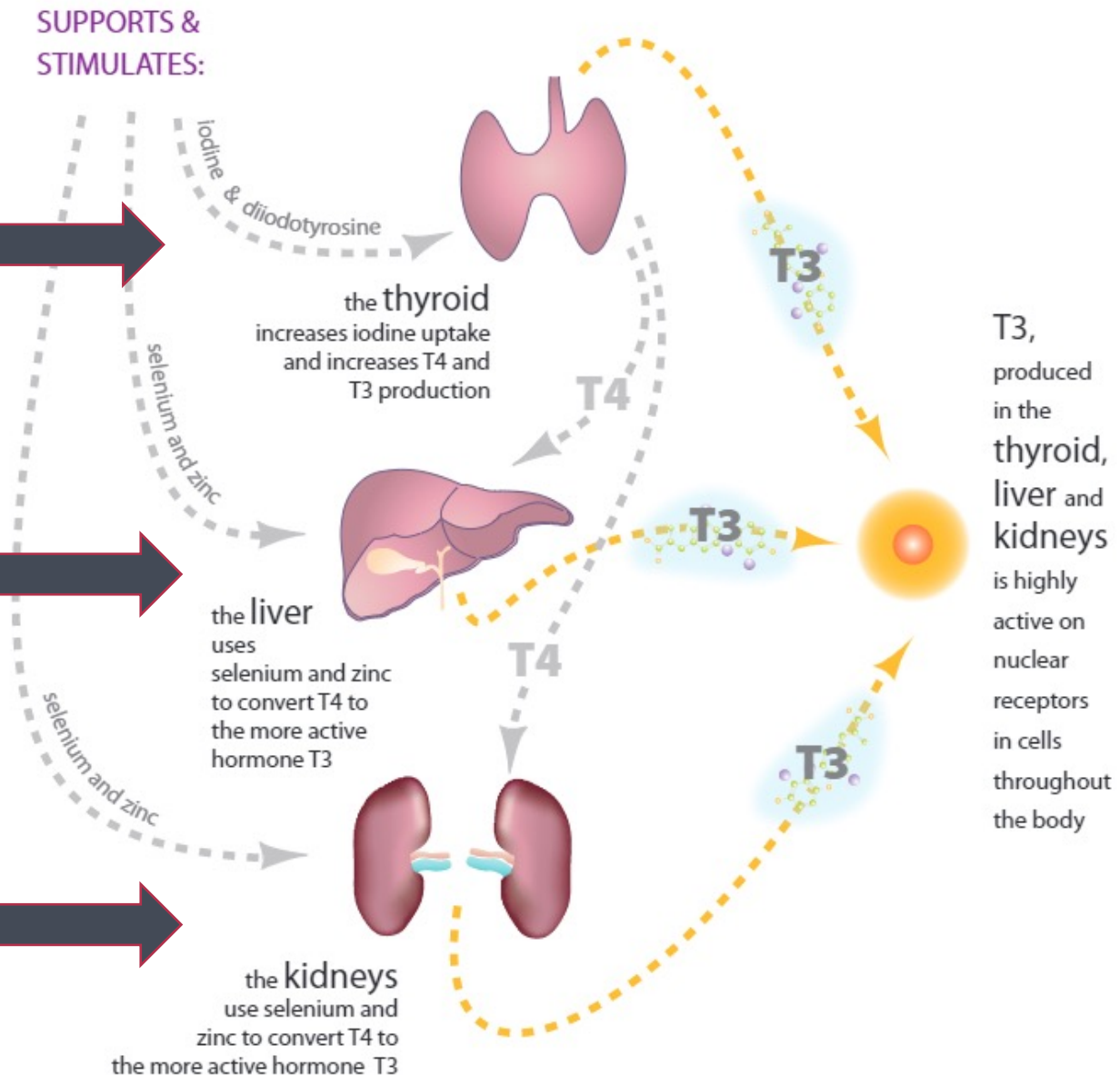
Improve overall T4 (& T3) production

Optimize conversion T4 to T3

Improve T3, lower rT3



Journal of Restorative Medicine 2012 https://doi.org/10.14200/jrm.2012.1.1008

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Combinations that support production

Vitamins and minerals that help close the gap on nutrient deficiencies

L-Tyrosine targeted amino acid support (precursor for thyroid production)

Ashwagandha has been shown to positively impact hypothyroid function

- 2018 RCT found that Ashwagandha treatment effectively normalized serum thyroid during the 8-week treatment period (TSH, T3, T4 at $p < 0.001$)

SUPPLEMENT FACTS

Serving Size: Two Capsules
Servings Per Container: 60

Two Capsules Contain:		% DV
Vitamin C (as Ascorbic Acid)	200 mg	222%
Vitamin E (as d-Alpha Tocopheryl)	67 mg	447%
Vitamin B12 (as Methylcobalamin)	100 mcg	4,167%
Iodine (as Potassium Iodide)	225 mcg	150%
Zinc (as TRAACS® Zinc Bisglycinate Chelate)†	5 mg	45%
Selenium (as L-Selenomethionine)	100 mcg	182%
Copper (as Copper Citrate)	500 mcg	56%
L-Tyrosine	500 mg	*
Ashwagandha extract (KSM-66®)†† (root) (*Withania somnifera*)	90 mg	*

*Daily Value (DV) not established.

Other Ingredients: Hypromellose (derived from cellulose) capsule, Leucine, Silicon Dioxide.

†This product uses Albion's TRAACS® Zinc Bisglycinate Chelate. TRAACS is a registered trademark of Albion International, Inc. ††This product uses Ixoreal Biomed's KSM-66® Ashwagandha. KSM-66 Ashwagandha is a registered trademark of Ixoreal Biomed, Inc.

‡This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

J Altern Complement Med. 2018;24(3):243-248

Combinations that address T3 optimization

Vitamins and minerals that help close the gap on nutrient deficiencies

- Selenium support been found to help neutralize thyroid levels in TD and AITD
- Note: vitamin A (increased receptor sensitivity support)

L-Tyrosine targeted amino acid support

Ashwagandha

- Both direct impact on thyroid function and
- Adrenal support

Guggul

- Increase the uptake of iodine by the thyroid gland and enhance the activity of thyroid peroxidase enzymes resulting in improved T3 to T4 ratio

Curcumin (turmeric) & N-Acytyl-L-Cysteine (NAC)

- Reduce oxidative stress associated with increased rT3 production

Supplement Facts V2

Serving Size 4 Capsules
Servings Per Container 30

4 capsules contain	Amount Per Serving	% Daily Value
Vitamin A (as Palmitate)	2,500 IU	50%
Vitamin C (as Ascorbic Acid USP)	200 mg	333%
Vitamin E (as d-Alpha Tocopherol Succinate USP)	200 IU	667%
Iodine (from Potassium Iodide)	200 mcg	133%
Zinc (as TRAACS® Zinc Bisglycinate Chelate)	20 mg	133%
Selenium (from Selenium-enriched Yeast) (SelenoExcell®)	200 mcg	286%
Copper (as TRAACS® Copper Bisglycinate Chelate)	1 mg	50%
N-Acetyl-L-Cysteine USP	500 mg	*
L-Tyrosine USP	400 mg	*
Ashwagandha Root Extract (Standardized to contain 1.5% Withanolides)	300 mg	*
Guggul Resin (Standardized to contain 2.5% Guggulsterones)	150 mg	*
Turmeric Root Extract (Standardized to contain 95% Curcuminoids)	100 mg	*

* Daily Value not established

Other Ingredients: Natural Vegetable Capsules, Microcrystalline Cellulose, Magnesium Stearate, Calcium Silicate, and Silicon Dioxide.

Journal of Restorative Medicine 2012

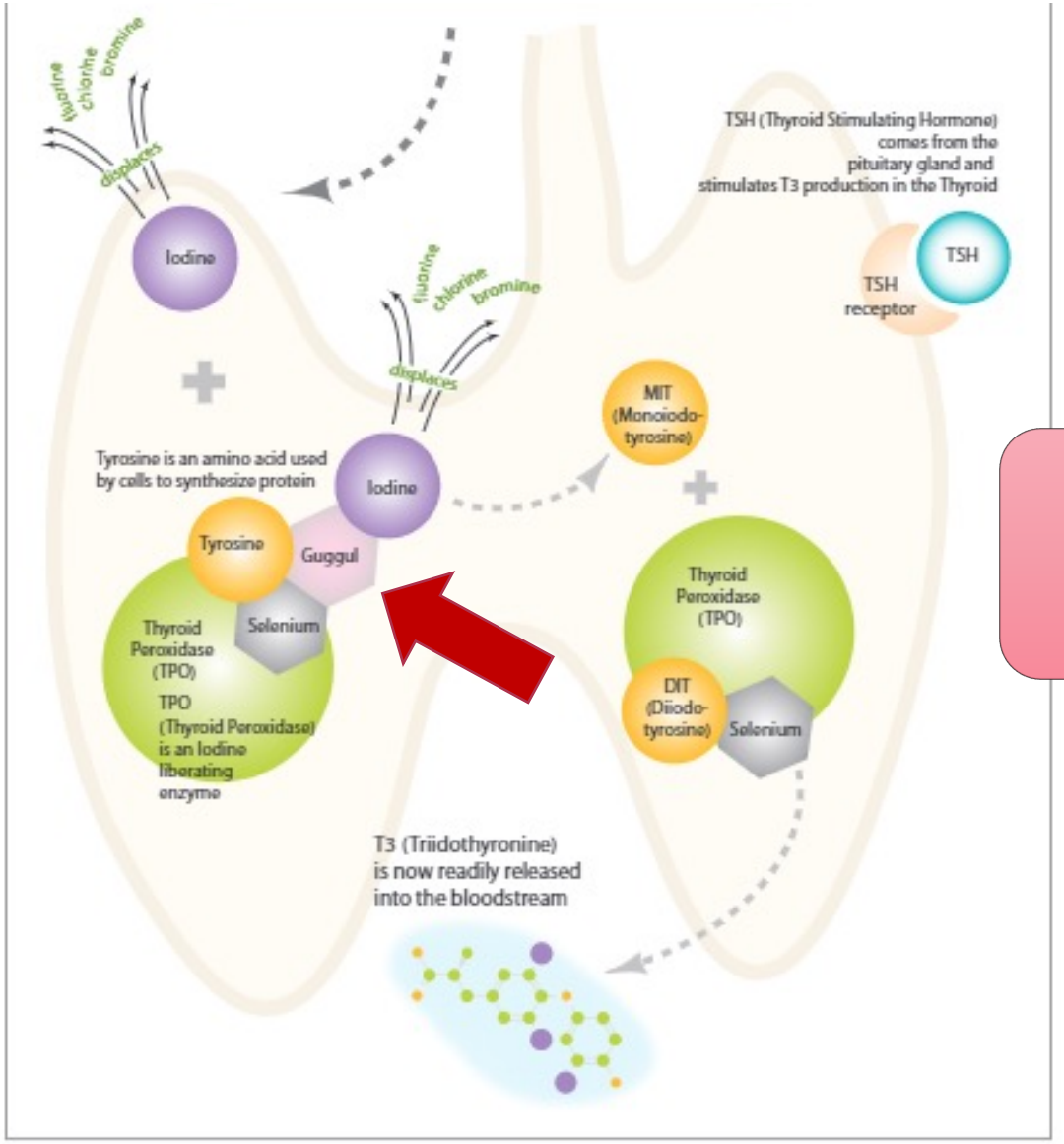
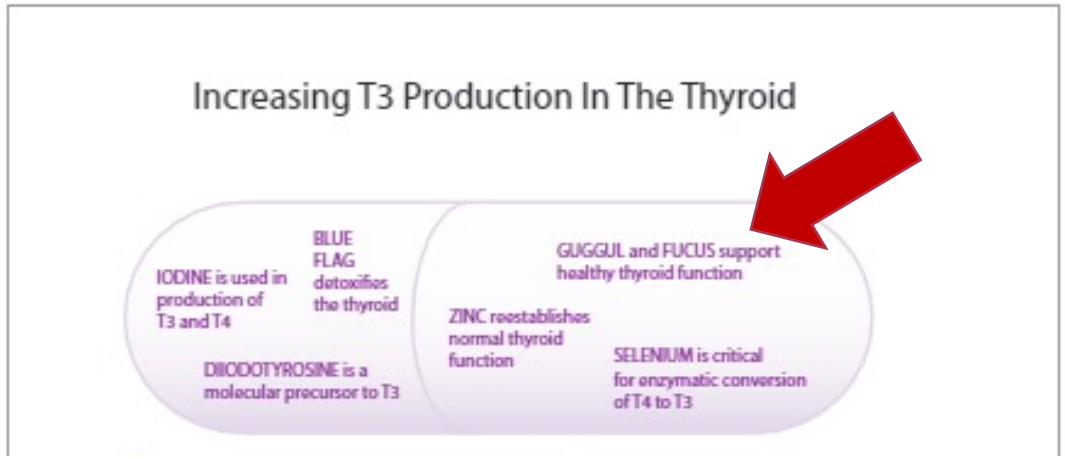


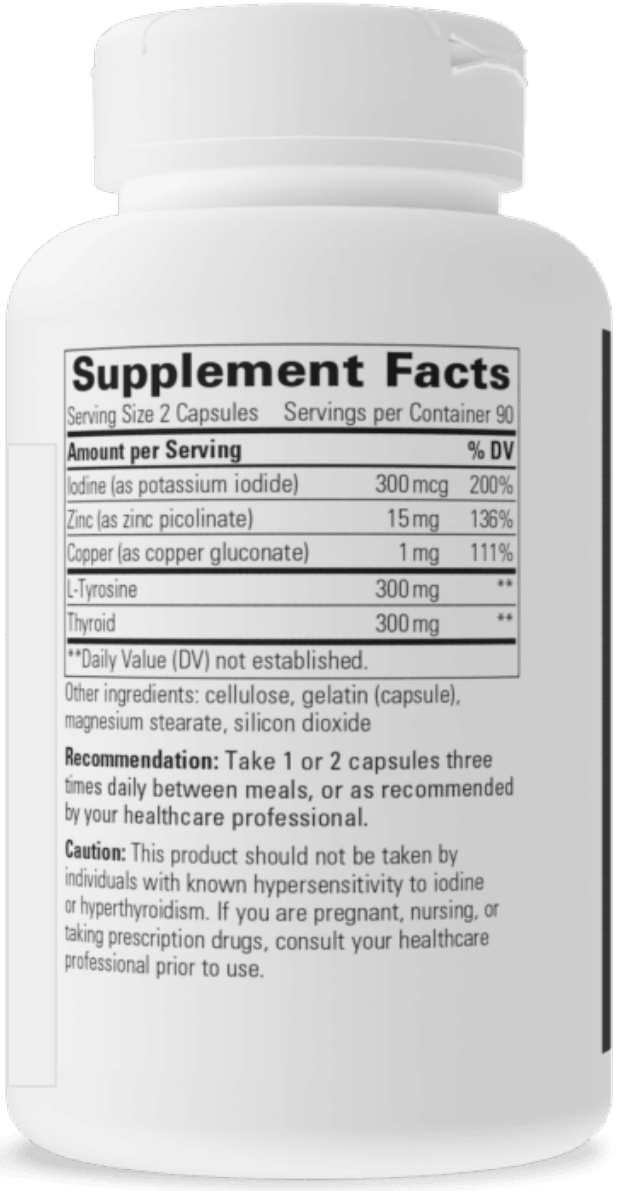
Figure 1

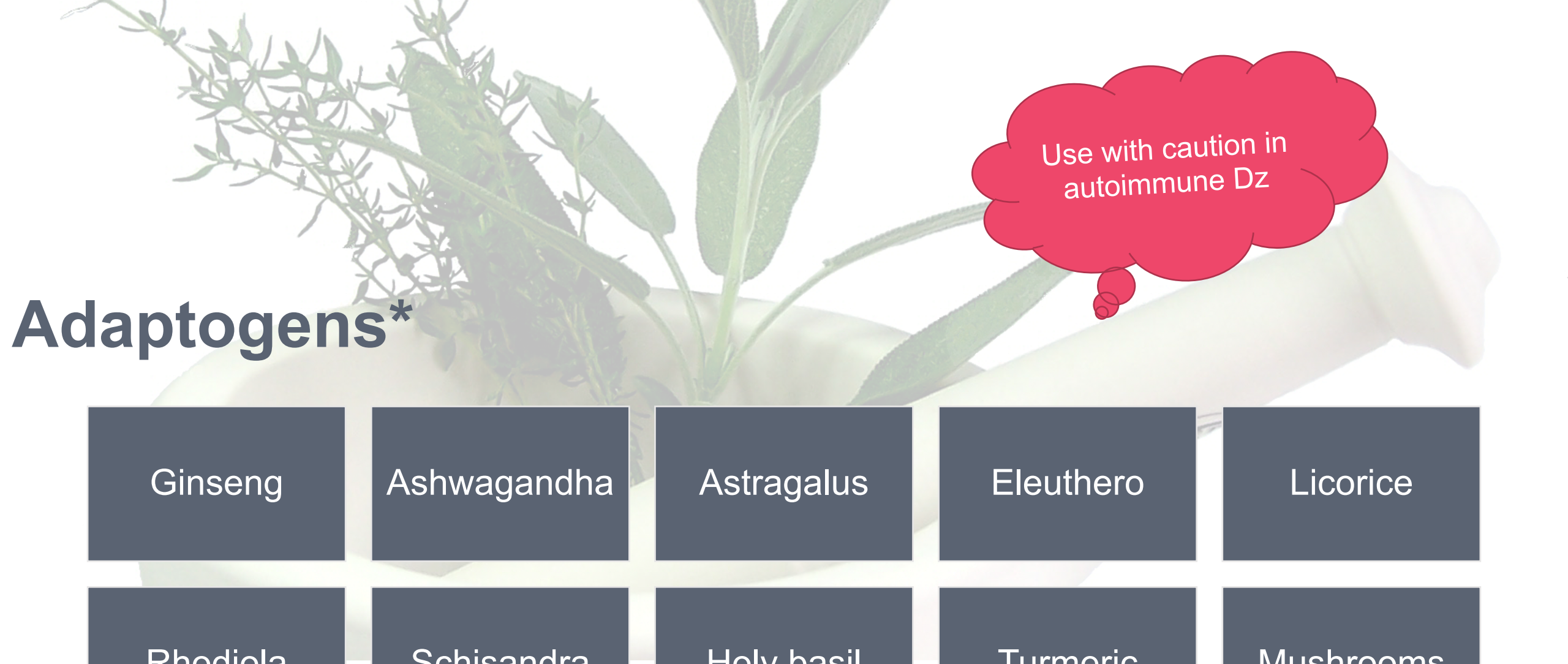


Guggul, when administered with tyrosine, selenium, iodine and other cofactors can help improve T3 production

Desiccated thyroid

- OTC thyroid complex available from multiple professional companies
- Use with caution
- Does not replace HRT Rx
- May be useful in cases of adrenal exhaustion accompanied by subclinical hypothyroidism
- Typically derived from porcine*





Use with caution in autoimmune Dz

Adaptogens*

Ginseng	Ashwagandha	Astragalus	Eleuthero	Licorice
Rhodiola	Schisandra	Holy basil	Turmeric	Mushrooms

Back to Amanda

Three months later, she comes back with a prescription for levothyroxine 25 mcg. What would you suggest as adjunctive support?

Type your answers into the chat box

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Dietary Considerations

The diet Rx for hypothyroidism

Comparative Study > J Coll Physicians Surg Pak. 2017 Jun;27(6):329-333.

Insulin Resistance and Glucose Levels in Subjects with Subclinical Hypothyroidism

Sikandar Hayat Khan [1], Nadeem Fazal [2], Aamir Ijaz [3], Syed Mohsin Manzoor [1], Naveed Asif [3], Tariq Rafi [3], Muhammad Yasir [2], Najmusaquib Khan Niazi [4]

Abstract

Objective: To compare insulin resistance and glycemic indicators among subjects with euthyroidism and subclinical hypothyroidism.

Study design: Comparative cross-sectional study.

Place and duration of study: Department of Pathology and Medicine, PNS Haf collaboration with the Department of Chemical Pathology and Endocrinology at Institute of Pathology (AFIP), Rawalpindi, from December 2015 to September 20

Methodology: Subjects referred for executive screening of apparently healthy population (without any known history of diabetes, hypertension, heart disease or other chronic ailments), were included. Subjects were grouped as euthyroidism and subclinical hypothyroidism.

Results: Median (IQR) insulin resistance indices including fasting insulin and Homeostasis Model Assessment for Insulin Resistance in subjects with group-1 (n=176, 87%, Thyroid Stimulating Hormone: 0.5 - 3.5 mIU/L) and group-2 (n=26, 13%, Thyroid Stimulating Hormone: 3.51 - 15 mIU/L) were 7.6 (6.70) vs. 11.4 (13.72, p=0.040) and 1.77 (1.79) vs. 2.8 (3.07, p=0.071). The median differences for fasting plasma glucose were 5.0 (1.0) in group-1 vs. 5.0 (1.47) for Group-2 [p=0.618], and glycated hemoglobin was 5.60 (1.1) vs. 5.60 (1.7, p=0.824). Homeostasis Model Assessment for beta sensitivity index in paradox showed slightly higher values for group-2 [median (IQR) 86.67 (92.94)] than group-1 [111.6 (189.64, p= 0.040)].

Conclusion: Measures of insulin resistance including Homeostasis Model Assessment for Insulin Resistance and fasting insulin levels were significantly different between subjects with euthyroidism and having subclinical hypothyroidism.

Conclusion: Measures of insulin resistance including Homeostasis Model Assessment for Insulin Resistance and fasting insulin levels were significantly different between subjects with euthyroidism and having subclinical hypothyroidism.

J Coll Physicians Surg Pak. 2017;27(6):329-333

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Review

Thyroid-Modulating Activities of Olive and Its Polyphenols: A Systematic Review

Kok-Lun Pang [1,†], Johanna Nathania Lumintang [2,†] and Kok-Yong Chin [1,*]

Abstract: Olive oil, which is commonly used in the Mediterranean diet, benefits related to the reduction of the risks of cancer, coronary heart dis neurodegenerative disease. These unique properties are attributed to the phy antioxidant activities in olive oil. Olive leaf also harbours similar bioacti studies have reported the effects of olive phenolics, olive oil, and leaf extr thyroid activities. A systematic review of the literature was conducted to i on the effects of olive derivatives on thyroid function. A comprehensive in October 2020 using the PubMed, Scopus, and Web of Science database human studies reporting the effects of olive derivatives, including olive leaf extracts on thyroid function were considered. The literature search fo topic, but only nine articles were included based on the inclusion and exclus articles were animal studies involving the administration of olive oil, oli pomace residues orally. These olive derivatives were consistently demonstrated to have thyroid-stimulating activities in euthyroid or hypothyroid animals, but their mechanisms of action are unknown. Despite the positive results, validation of the beneficial health effects of olive derivatives in the human population is lacking. In conclusion, olive derivatives, especially olive oil and leaf extract, could stimulate thyroid function. Olive pomace residue is not suitable for pharmaceutical or health supplementation purposes. Therapeutic applications of olive oil and leaf extract, especially in individuals with hypothyroidism, require further validation through human studies.

- Human studies lacking, but promising and logical suggestion
- Olive derivatives involved in stimulating the thyroid hormones (exact mechanism unknown)
- Improvement of thyroid function and oxidative status due to polyphenols and antiinflammatory compounds
- Olive oil and leaf extract are also postulated to induce a higher rate of conversion of inactive T4 to biologically active T3

Nutrients. 2021;13(2):529

Nutrition is the relationship between…

- Macronutrients
- Micronutrients
- Phytonutrients

- The microbiome
- Your genetics
- The environment
- Your intention

nutrients

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Review

Thyroid-Gut-Axis: How Does the Microbiota Influence Thyroid Function?

Jovana Knezevic [1], Christina Starchl [1,*], Adelina Tmava Berisha [2] and Karin Amrein [1]

Abstract: A healthy gut microbiota not only
but also on thyroid function. Thyroid an
thyroiditis (HT) and Graves' disease (GD
(AITD) and often co-occur with Celiac Di
This can be explained by the damaged inte
permeability, allowing antigens to pass mo
with extraintestinal tissues, respectively. D
been reported in thyroid carcinoma, in whic
bacterial strains were observed. Additionall
on the availability of essential micronutrients
for thyroid hormone synthesis, selenium a
D assists in regulating the immune respons
in AITDs, resulting in malfunctioning of t
absorption of these nutrients and further in
and T3 levels. Supplementation of probiotics showed beneficial effects on thyroid hormones and thyroid function in general. A literature research was performed to examine the interplay between gut microbiota and thyroid disorders that should be considered when treating patients suffering from thyroid diseases. Multifactorial therapeutic and preventive management strategies could be established and more specifically adjusted to patients, depending on their gut bacteria composition. Future well-powered human studies are warranted to evaluate the impact of alterations in gut microbiota on thyroid function and diseases.

Dysbiosis is associated with AITD as well as certain cancers

Dysbiosis and intestinal permeability are also associated with nutrient deficiencies, malabsorption

…the interplay between gut microbiota and thyroid disorders that should be considered when treating patients suffering from thyroid diseases. Multifactorial therapeutic and preventive management strategies could be established and more specifically adjusted to patients, depending on their gut bacteria composition.

Nutrients. 2020;12(6):1769

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Review

Thyroid-Gut-Axis: How Does the Microbiota Influence Thyroid Function?

Jovana Knezevic [1], Christina Starchl [1,*], Adelina Tmava Berisha [2] and Karin Amrein [1]

Yes, AITD *(we know that already, right?)*

Dysbiosis impacts the nutrient status of key micronutrients including Iron, selenium, iodine, vit A and others

Dysbiosis also impacts digestion of macronutrients as well, including amino acids (think essential AA phenylalanine and conditionally essential tyrosine)

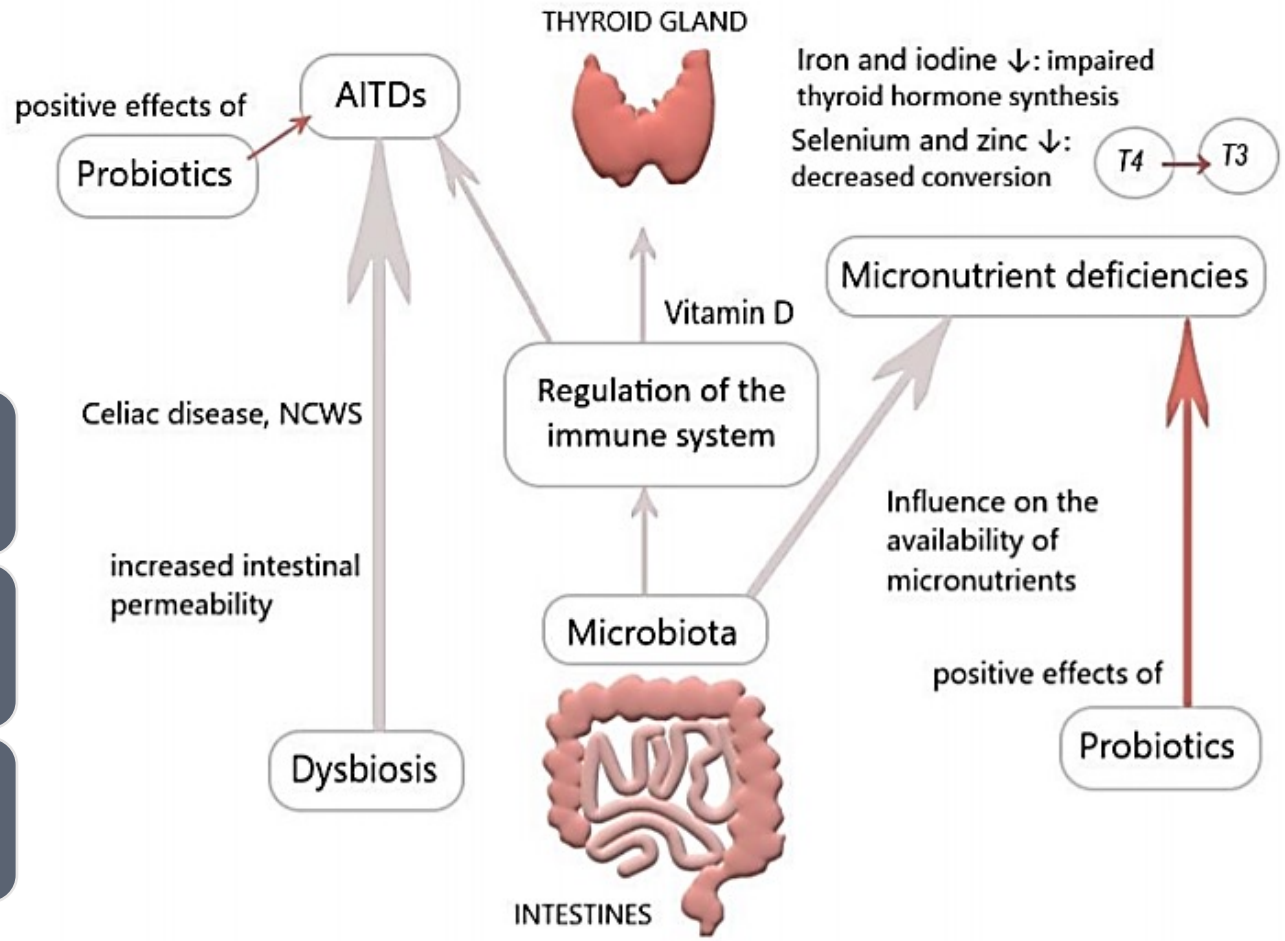

Figure 1. Overview of the influence of the gut on the thyroid (personal figure).

frontiers in Medicine

PERSPECTIVE
published: 18 April 2018
doi: 10.3389/fmed.2018.00109

Front Med (Lausanne). 2018;5:109

Immune Cells and Microbiota Response to Iron Starvation

Marcello Chieppa* and Gianluigi Giannelli

National Institute of Gastroenterology "S. de Bellis", Research Hospital, Castellana Grotte, Italy

Metal ions are essential for life on Earth, mostly as crucial components of all living organisms; indeed, they are necessary for bioenergetics functions as crucial redox catalysts. Due to the essential role of iron in biological processes, body iron content is finely regulated and is the battlefield of a tug-of-war between the host and the microbiota.

Keywords: iron-chelating agents, microbiota, inflammation, inflammatory bowel disease, immune cells

Iron availability in the intestinal lumen could prevent or promote intestin
current data do not provide a definitive response. Recent data demons
polyphenols explicit their anti-inflammatory functions sequestrating
we discuss whether nutritional iron chelators could be able to change t
and prevent the intestinal dysbiosis associated with intestinal chronic

Iron is lost by cellular exfoliation and occasional bleeding; it is ab
ponents. Heme is the most important source of dietary iron, while n
only in the duodenum and the beginning of the jejunum in pH permis
diets often contain large quantities of foods characterized by a high
fish, and poultry, and small quantities of non-heme-iron content like vegetables, fruits, and nuts. Furthermore, nutritional substances can affect iron absorption: ascorbic acid is an efficient enhancer of non-heme-iron absorption, *vice versa*, phytic acid is known to be among the major iron absorption inhibitors, and iron-chelating substances like quercetin inhibit its absorption, likely due to loss of chelated-iron solubility.

Iron deficiency is the most common cause of anemia worldwide and one of the most common complications observed in inflammatory bowel disease (IBD) patients due to gastrointestinal hemorrhages. In IBD patients, the guidelines for the management of iron deficiency are not entirely satisfactory because following oral iron supplementation patients sometimes report worsening of the IBD symptoms (1). Interestingly, iron supplemented diets can also show protective effects in dextran sodium sulfate (DSS)-induced colitis models. Constante et al. demonstrated that iron formulation dramatically changed the outcome of the DSS-induced colitis, as oral supplementation with ferrous bisglycinate but not ferric ethylenediaminetetraacetic acid enhanced the beneficial action of probiotics (2).

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Chenyang Wang, Nanjing University, China

****Correspondence:***
Marcello Chieppa
transmed@irccsdebellis.it

Thyroid function is directly and indirectly linked to microbiome → one relationship is through iron balance

- The relation between iron availability and intestinal microbiota is still largely unexplored although it is well known that iron availability influences the composition of the microbiota.
- Furthermore, iron levels directly impact thyroid activity

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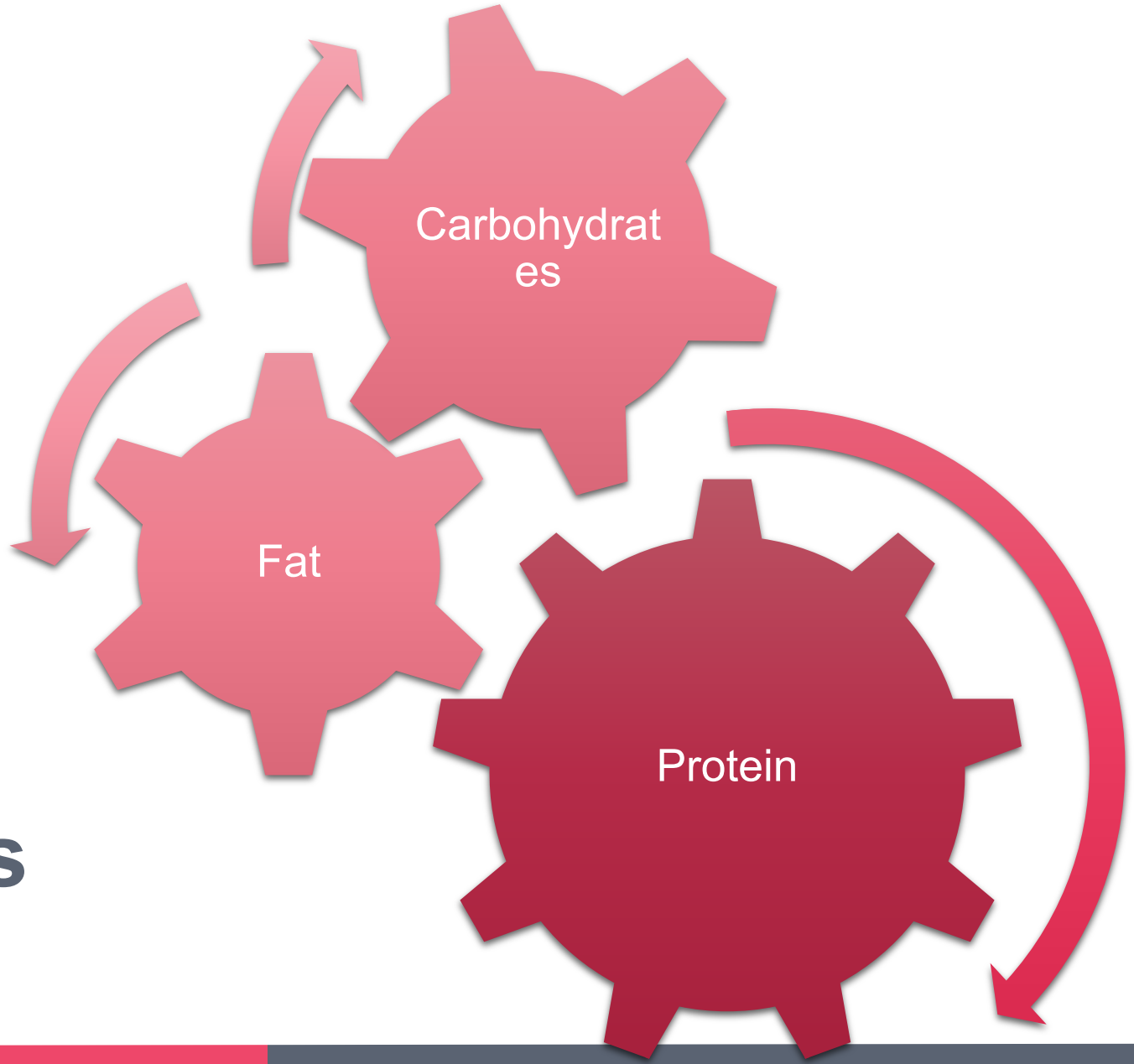
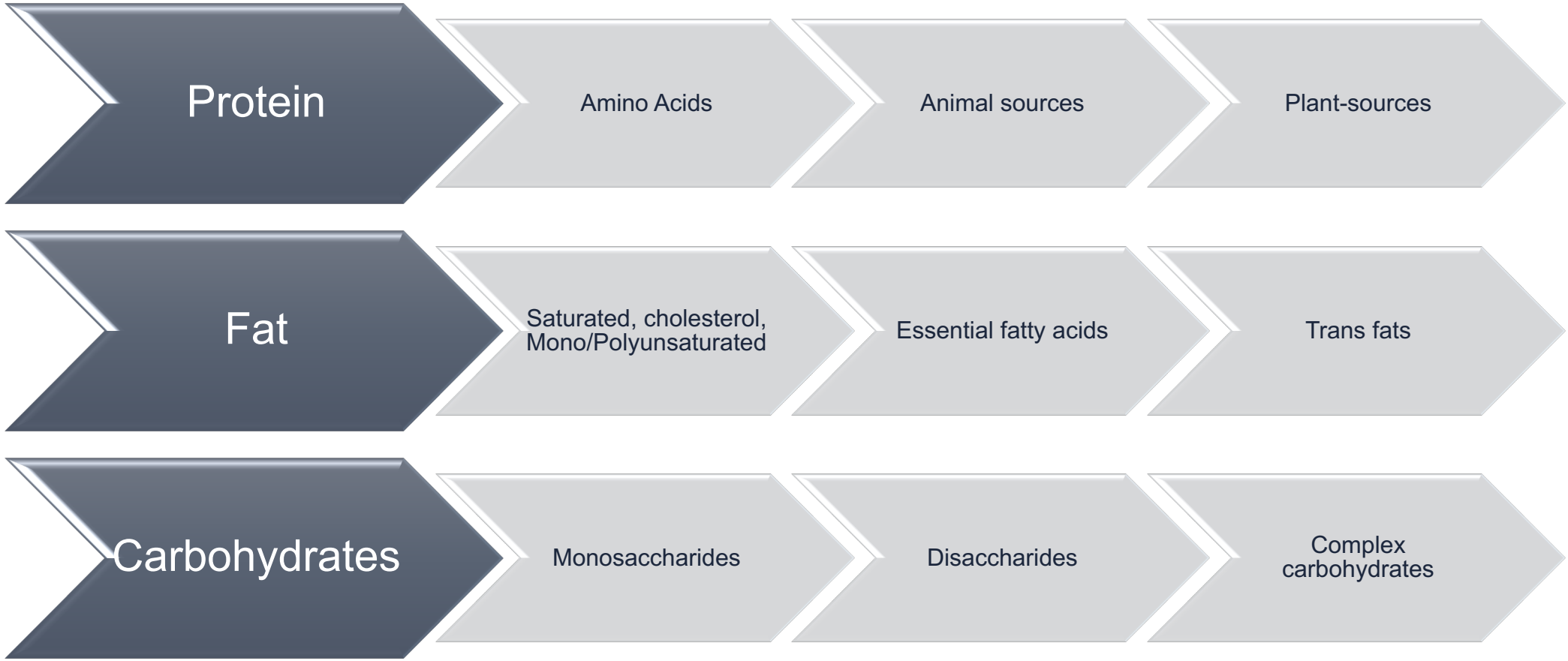
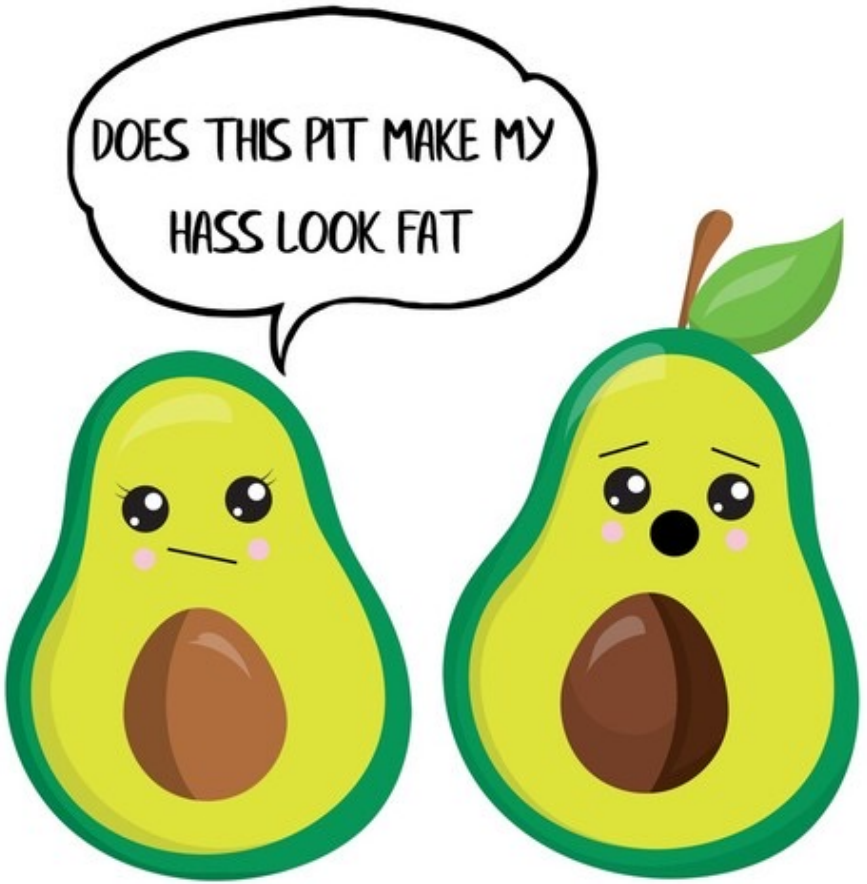
Macronutrients



Macronutrients




DOES THIS PIT MAKE MY
HASS LOOK FAT

The Misunderstood Macronutrient: Fats

Benefits of healthy fats like nuts, seeds, avocado and olives associated with:

- Improved blood sugar balance
- Favorable modulation of the microbiome
- Phytochemicals known to modulate immune response

Protein & Amino Acids

Animal protein vs plant protein

- Plants > animal sources
- Animal sources > plants

Sources of Iron

- Heme vs non-heme (and a note on “anti-nutrients”)
- Broccoli, leafy greens, mushrooms, soybeans (tofu, tempeh, natto), legumes, quinoa, pumpkin, sesame and flaxseeds .. DARK CHOCOLATE!
- Animal meat, poultry, eggs, liver, shellfish & fish

Amino acids

- Complete proteins (ex grains + legumes)

Nutrients **2013**, *5*, 4642-4652; doi:10.3390/nu5114642

OPEN ACCESS

nutrients

ISSN 2072-6643

www.mdpi.com/journal/nutrients

Article

Vegan Diets and Hypothyroidism

Serena Tonstad [1,2,*], Edward Nathan [3], Keiji Oda [4] and Gary Fraser [5,6]

Abstract: Diets eliminating animal products have rarely been as
hypothyroidism but may protect against autoimmune disease. Thus, we inves
risk of hypothyroidism was associated with vegetarian compared to omn
patterns. The Adventist Health Study-2 was conducted among church mer
America who provided data in a self-administered questionnaire. Hypot
queried at baseline in 2002 and at follow-up to 2008. Diet was examined as a
prevalent (n = 4237 of 65,981 [6.4%]) and incident cases (1184 of 41,
multivariate logistic regression models, controlled for demographics and
prevalence study, in addition to demographic characterstics, overweigh
increased the odds (OR 1.32, 95% CI: 1.22–1.42 and 1.78, 95% CI: 1.64–1.93, respectively). Vegan *versus* omnivorous diets tended to be associated with reduced risk (OR 0.89, 95% CI: 0.78–1.01, not statistically significant) while a lacto-ovo diet was associated with increased risk (OR 1.09, 95% CI: 1.01–1.18). In the incidence study, female gender, white ethnicity, higher education and BMI were predictors of hypothyroidism. Following a vegan diet tended to be protective (OR 0.78, 95% CI: 0.59–1.03, not statistically significant). In conclusion, a vegan diet tended to be associated with lower, not higher, risk of hypothyroid disease.

investigated whether risk of hypothyroidism was associated with vegetarian compared to omnivorous dietary patterns

Surprisingly, vegan diet even though lacking animal sources of iodine, was associated with lower risk of hypothyroidism

Lacto-ovo diet may increase risk (dairy?)

Unknown what other factors may have impacted outcomes

Fiber & Polyphenols

- Support the microbiome
- May cause digestive disturbances
- Gradually build up
- Variety is Queen

The Forgotten Macronutrient: Water

Drink clean **filtered** water, free of contaminants

½ body weight (lbs to oz) (the “pee test”)

Other sources include veggies, fruit, soup, herbal teas, carbonated water (not tonic)

Caffeine and alcohol are dehydrating

Hydrate more when physical demands are higher, exercise, or the weather is hot

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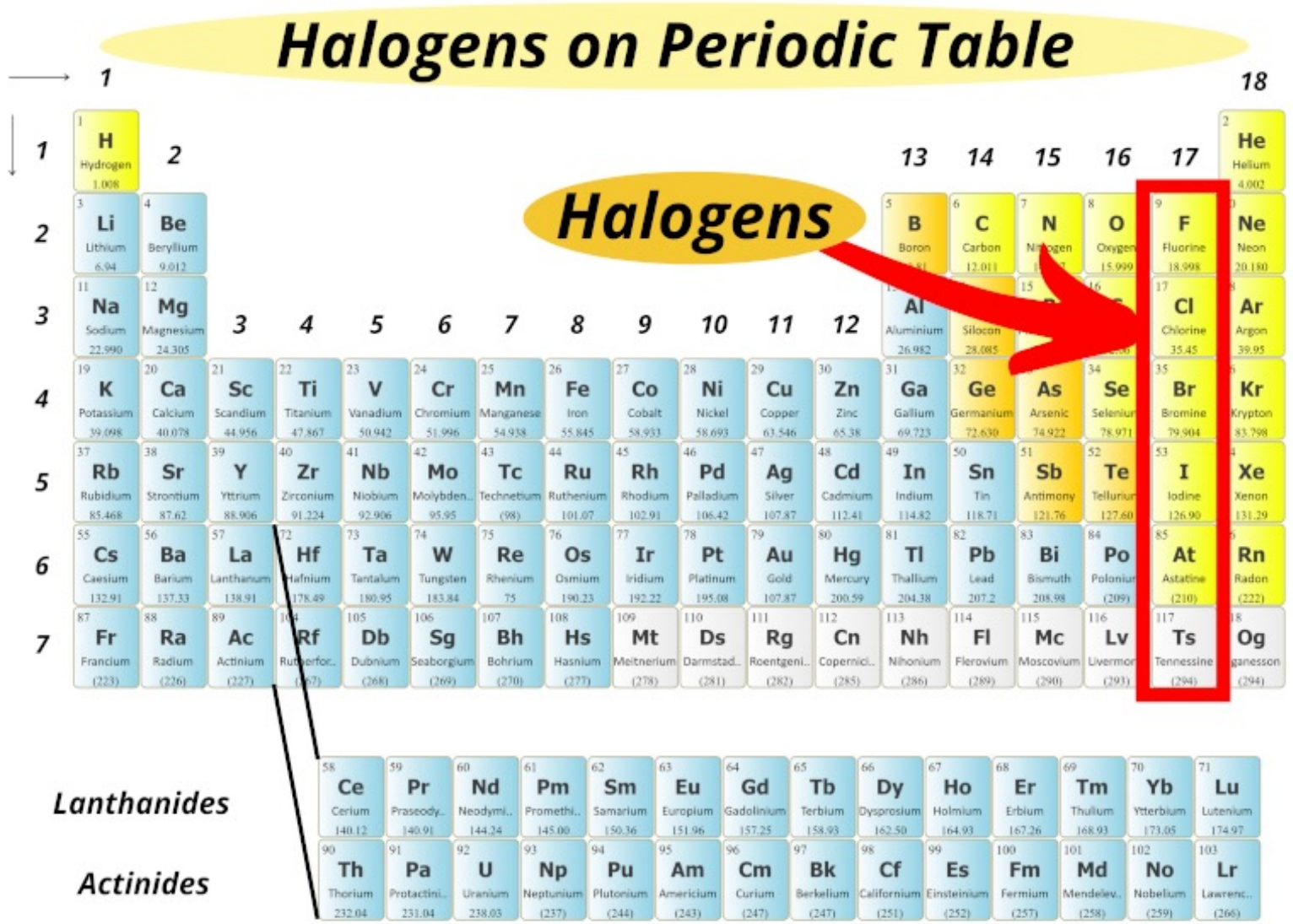
Halogens

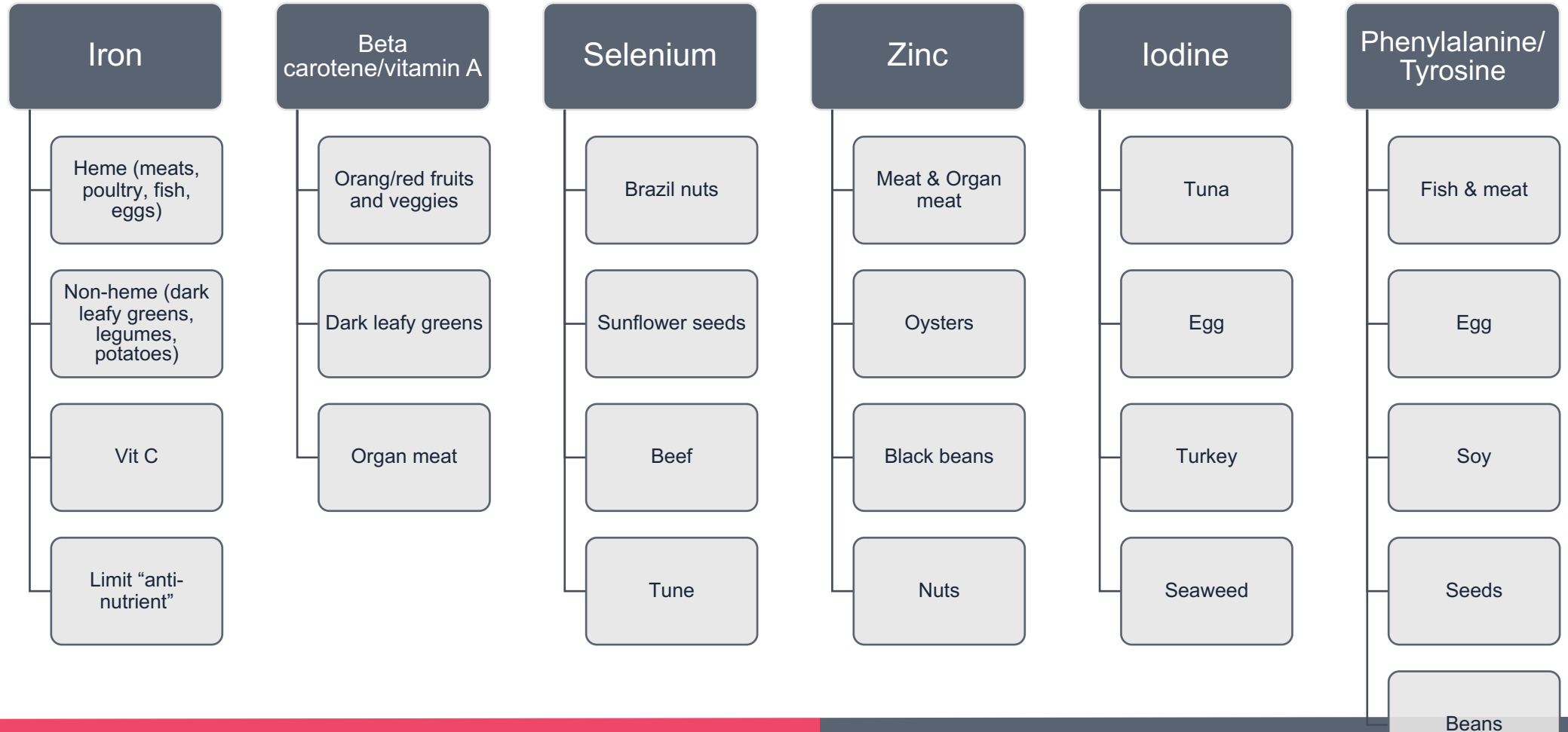


Micronutrients

Vitamins

Minerals

Food sources of thyroid specific nutrients



https://lpi.oregonstate.edu/mic/minerals/

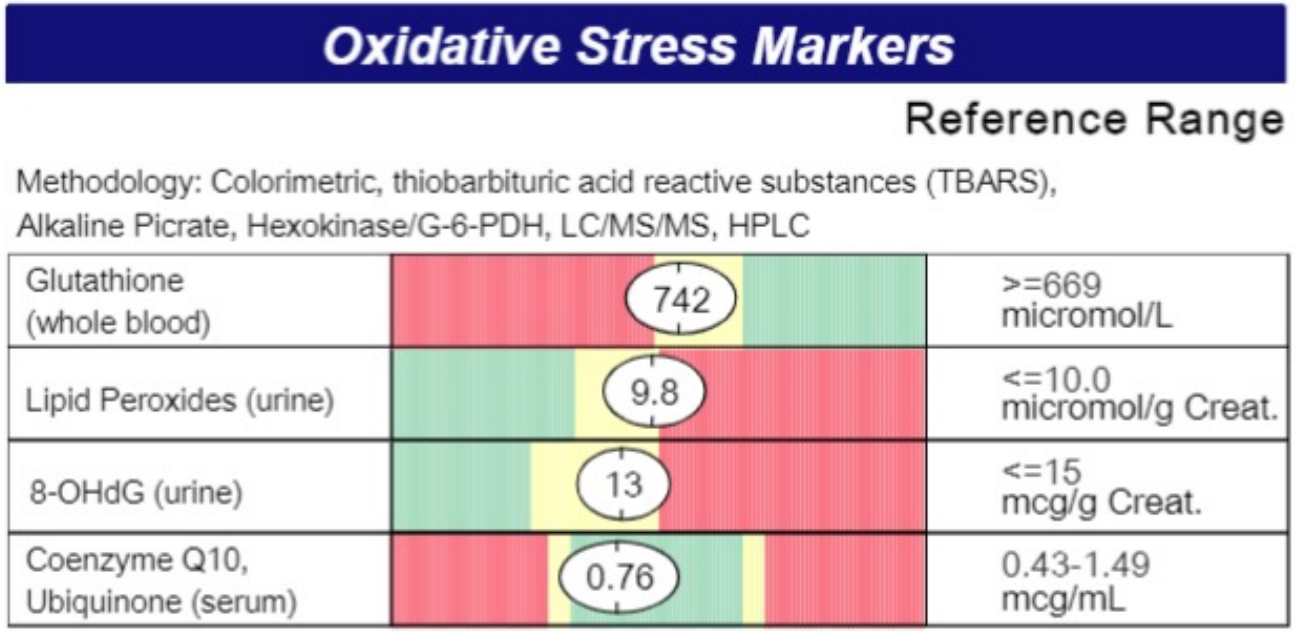
Digestive support

- Diaphragmic breathing
- Stress/trauma
- Chewing
- Digestive enzymes, bitters, and Betaine
- Bitter greens
- Bone broth
- Ginger

Other considerations

- Gut health
- Hormone health
- Oxidative stress & detoxification

Oxidative Stress Markers

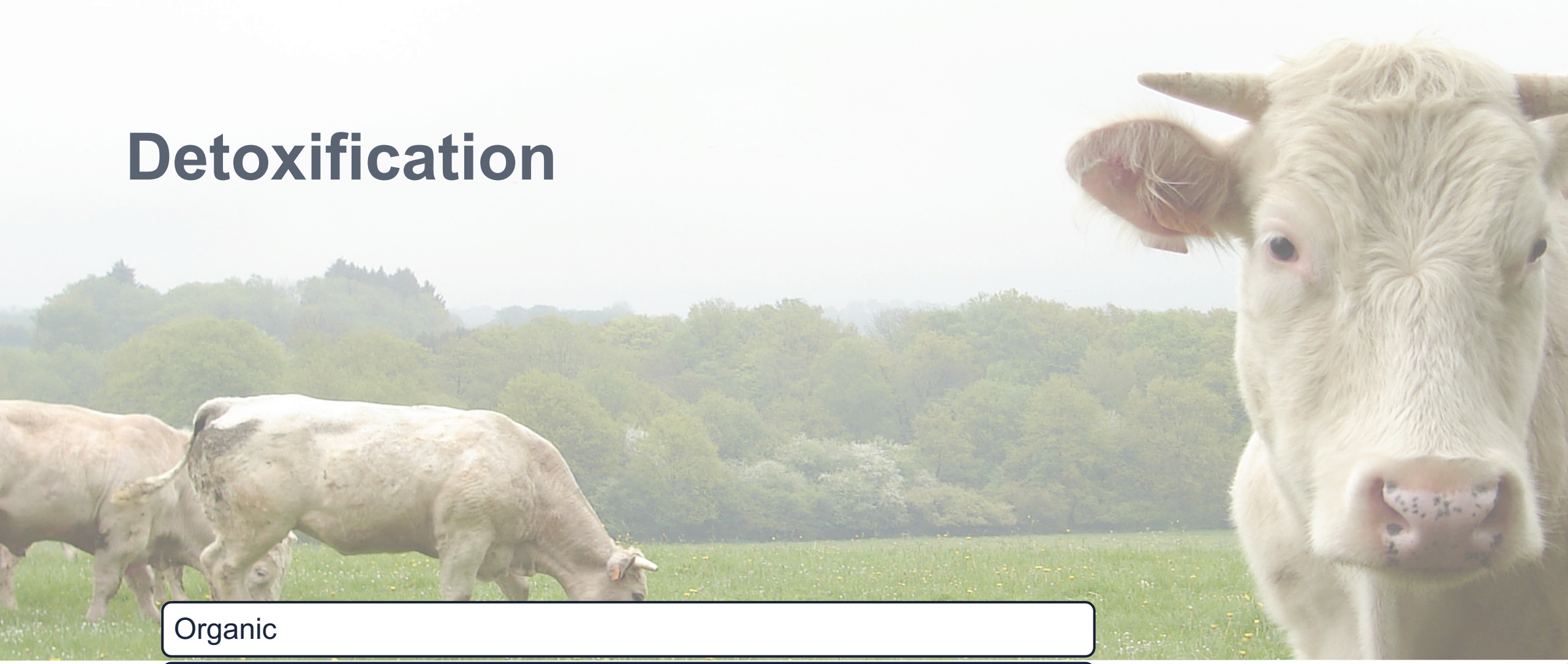


Detoxification

Not the same thing as a cleanse or “tea”

Normal part of the way our body removes toxins/toxicants

Detoxification



- Organic
- Hormone-free
- Grass-fed
- Pasteur-raised, free-range

Antioxidants

Neutralize ***oxidative stress***

“Fire fighters”

Examples

- Vitamins including vit C, Vit A/beta carotene, Vit E
- Minerals like selenium and zinc
- NAC and glutathione supportive foods
- Fish oil
- Alpha linoleic acid

Nrf2 and ARE

The Nrf2-Antioxidant Response Element Signaling Pathway and Its Activation by Oxidative Stress*

Published, JBC Papers in Press, January 30, 2009, DOI 10.1074/jbc.R900010200

Truyen Nguyen[‡], **Paul Nioi**[‡], **and Cecil B. Pickett**[§1]

From the [‡]*Schering-Plough Research Institute, Summit, New Jersey 07901 and* [§]*Biogen Idec, Cambridge, Massachusetts 02142*

A major mechanism in the cellular defense against oxidative or electrophilic stress is activation of the Nrf2-antioxidant response element signaling pathway, which controls the expression of genes whose protein products are involved in the detoxication and elimination of reactive oxidants and electrophilic agents through conjugative reactions and by enhancing cellular antioxidant capacity. At the molecular level, however, the regulatory mechanisms involved in mediating Nrf2 activation are not fully understood. It is well established that Nrf2 activity is controlled, in part, by the cytosolic protein Keap1, but the nature of this pathway and the mechanisms by which Keap1 acts to repress Nrf2 activity remain to be fully characterized and are the topics of discussion in this minireview. In addition, a possible role of the Nrf2-antioxidant response element transcriptional pathway in neuroprotection will also be discussed.

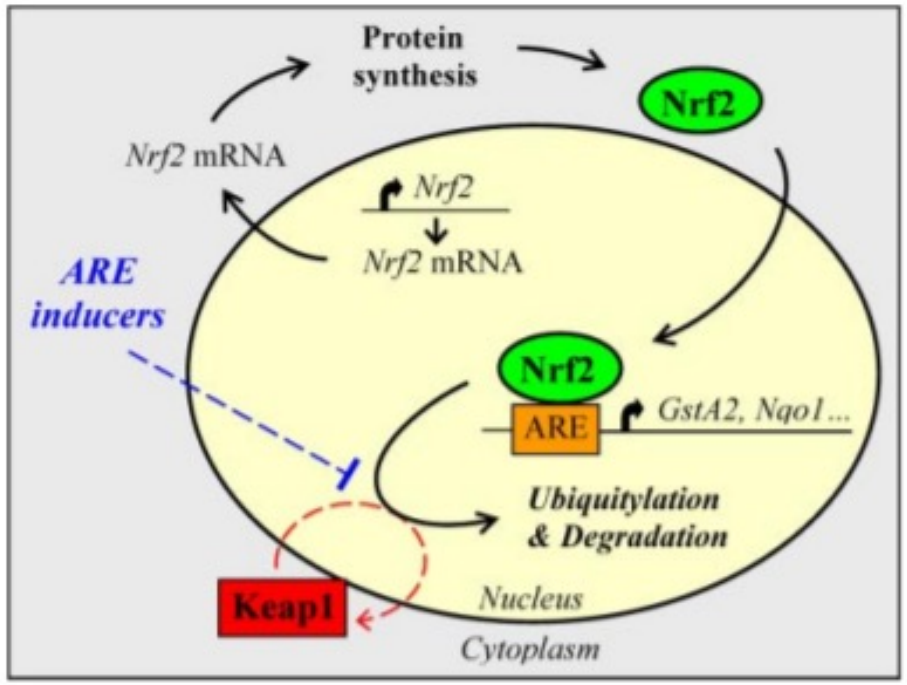


FIGURE 3. **Proposed Nrf2-ARE signaling pathway.** Nrf2 is expressed constitutively in the cell and translocates directly to the nucleus following its synthesis. Following transactivation of its genes, Nrf2 is targeted for degradation by Keap1 in the nucleus, a process that requires the transient shuttling of Keap1 into this compartment. In cells under stress, stabilization of Nrf2 is thought to be dependent on mechanisms that either prevent or reduce access of Keap1 to Nrf2. This figure was reproduced from Ref. 12.

J Biol Chem. 2009;284(20):13291-13295

Foods that Support Detoxification & Reduce Oxidative Stress/antioxidants

Allium foods

- Garlic, onion, leek, shallots, scallions, spring onions, and chives

Cysteine & methionine sources

- Lean meats, fish, lentils, oats, eggs, sunflower seeds

Fiber

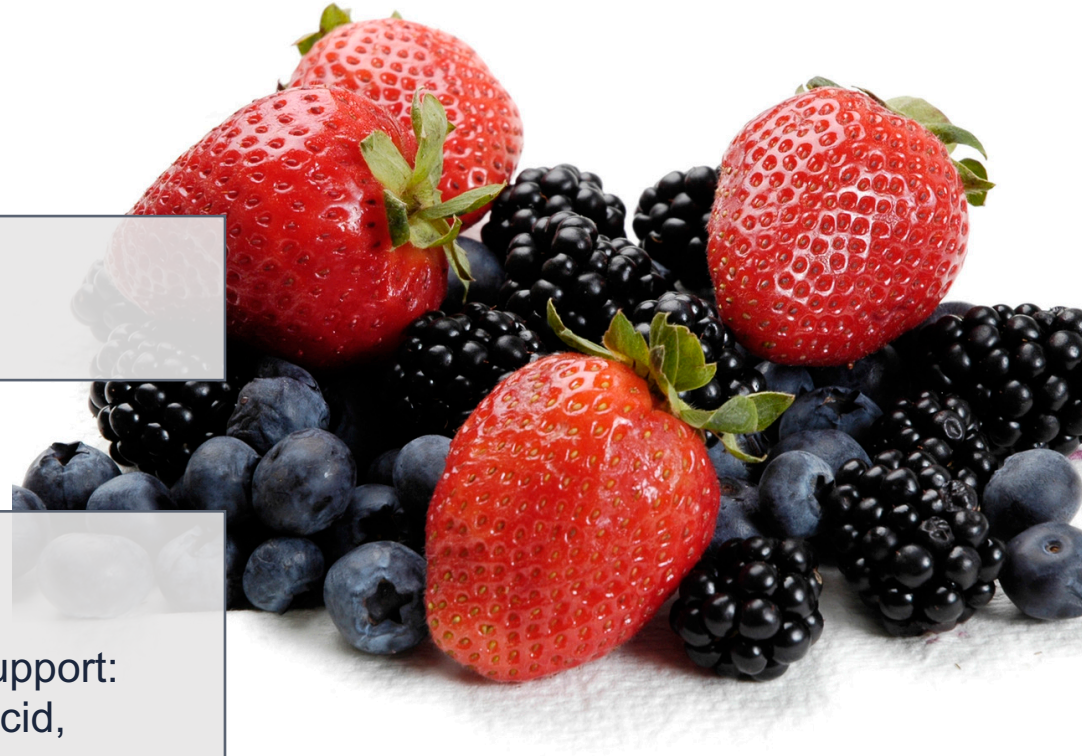
- Root veggies, leafy greens, fruits and veggies in general, grain and legumes

Methylation/hormone detoxification support

- Egg yolks, liver, beets, mushrooms, dark leafy greens, broccoli and garlic

Phytonutrients

Color “eat the rainbow”



Phytonutrients can contribute to synergistic support including:

- Thyroid, adrenals, GI, immune and detoxification support:
- Resveratrol, EGCG, curcumin, flavonoids. Ellagic acid, phytoestrogens, Glucosinolates etc…

Meal Timing

Intermittent fasting

Time Restricted Eating

Fasting and modified fasting

Controversies in dietary approach to TD

- Elimination diet, including gluten and dairy (among other food sensitivities)
- Vegan vs paleo vs keto
- Lectins and “anti-nutrients”

FUNCTIONAL MEDICINE
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What about Amanda?

Addressing the underlying metabolic issue was a key factor in improving her fertility

Along with fertility support, GI support and dietary changes, thyroid support led to successful pregnancy

In Summary

1. There are four main pathophysiological categories in thyroid disease including hypo-, hyperthyroidism, autoimmune
2. Adrenal and hormone health are an important consideration when optimizing thyroid health and may contribute to adrenal-related dysfunction
3. Symptoms of thyroid disease can be due to inadequate production of hormone, inadequate activation, excess inactive hormone, and thyroid resistance (or a combination of)
4. Pharmacists can play a major role in assessment and recognizing thyroid disease in the undiagnosed population
5. DIND is a major opportunity for pharmacists to intervene with nutrient optimization to protect thyroid health
6. There are multiple nutrients and herbs available to support optimal thyroid function
7. Nutraceuticals can often be used safely and effectively in combination with HRT to optimize thyroid health
8. Foundational dietary interventions should be discussed with patients to support thyroid function, and…
9. A full FxMed approach should also keep in mind that GI health, oxidative stress, detoxification, adrenal and hormone health should also be optimized.

Thank you!

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