Thyroid – New Trends

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Paradigms: Shift Happens

- All scientific discoveries go through 3 phases
  - 1. Ridicule
  - 2. Violent opposition
  - 3. Truth considered to be self-evident
    - Examples

Objectives

- Dispel the Myths
- Historical Perspective on Thyroid Treatment and Monitoring
- ATA & AACE Guidelines
- Discuss Thyroid Hormones & Deiodonases
- Signs and Symptoms of Hypothyroidism
- Causes & Types of Hypothyroidism
- Lab Values
- Treatment Options
- Thyroid & Disease Processes/Risk Factors
- Hashimoto’s Thyroiditis
- Iodine & the Thyroid

Thyroid Myths

MYTH 1: T4 is good, T3 is bad (only has negative clinical effects)

- T3 is a molecule present from birth in every human's body
- T3 is essential to life
- NO studies have shown T3 damages heart, brain or any other tissues

MYTH 2: T3 will cause atrophy to the gland causing permanent dependence on thyroid hormone replacement

- NO evidence has ever shown that is damages a previously healthy gland to prevent normal function when medicine discontinued

MYTH 3: Suppressing TSH will cause osteoporosis

- Hyperthyroid disease (Graves') from too much ENDOGENOUS production of thyroid hormone IS linked to bone loss
- NO study has shown adequate/upper limit T3 levels are linked to bone loss

MYTH 4: Once you start thyroid, you will need it the rest of your life

- Not true (unless partial or full removal of the gland)

Traditional Perspective on Thyroid Treatment

- Assumption that normalization of TSH can be done with T4 only (Tested in 2 Studies 1986 & 1996)
- Findings:
  - T4 could maintain T3 in the pituitary (hence the normal TSH)
  - Virtually all other tissues had low T3 concentrations
  - Suppressed or undetectable TSH did not indicate (nor was it a reliable marker of) over-replacement or hyperthyroid
  - Suppressed TSH indicated overreplacement about 16% of the time

Escobar-Morreale, H.F.; del Rey, F.E.; Obregón, M.J.; de Escobar, G.M., 1996: Only the combined treatment with thyroxine and triiodothyronine ensures euthyroidism in all tissues of the thyroidectomized rat. *Endocrinology* 137(6): 2490-2502

Fraser WD, Biggart EM, OReilly DJ, Gray HW, McKillop JH; 1986: Are biochemical tests of thyroid function of any value in monitoring patients receiving thyroxine replacement?. *The British Medical Journal* 293:808-810

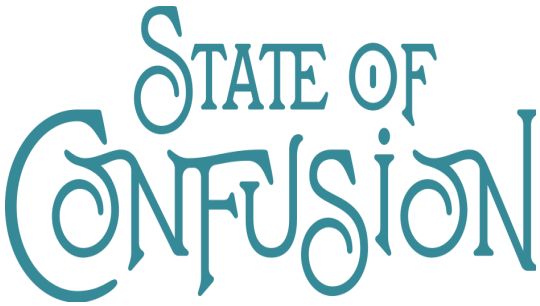
AACE-ATA Hypothyroidism Guidelines

- **Clinical Scoring systems should not be used for diagnosis**
  - Treatment should be considered if the patient **has symptoms suggestive of hypothyroidism** or + TPO or evidence of atherosclerotic disease, heart disease
- Free Hormone Hypothesis: only free hormone is metabolically active, therefore **only free hormone determines thyroid status**
  - **Serum Free T3 should not be used to diagnose hypothyroidism**
- Hypothyroid patients with normalized TSH still more likely to feel poorly

AACE-ATA Hypothyroidism Guidelines

- Most studies used to invoke the benefit of treating or preventing atherosclerotic disease used markers and not cardiovascular events as endpoints
  - UK General Practitioner “in the 50% of individuals 40-70 treated with L-thyroxine, the hazard radio for cardiac events was reduced”
  - Cleveland Clinic: patients under 65, not treated with thyroid hormone had higher all cause mortality
- 50% of patients with TSH between 2.5-4.5 range may have thyroid disease and 50% may not “If its not broke, don’t fix it”
- Use of combo therapy (desiccated thyroid): “**We don’t yet understand patient preference for combinations**”
  - Patients should be treated with L-thyroxine monotherapy
- Why not treat everyone? – Risks of overtreatment- more adverse effects with **poor monitoring**

Practice Guidelines Take Home



- Clinical scoring systems shouldn't be used, but treatment should be considered if the patient has symptoms suggestive of hypothyroidism
- Only free hormone determines thyroid status, but we should not use free T3 to diagnose hypothyroidism
- ½ patients with TSH between 2.5-4.5 may be hypothyroid, but ½ may not, so we shouldn't treat because only ½ of them will actually be hypothyroid
- We don't understand why patients prefer NDT so we shouldn't use it
- We shouldn't treat everyone because adverse events can occur when we don't monitor them adequately

What?!?!

TSH is an excellent test except….

- Central disease
- Abnormal isoforms, TSH receptor polymorphisms
- Drugs (metformin, dopaminergic drugs, glucocorticoids…)
- Diurnal variation
- Adrenal insufficiency
- Age/ethnicity variations

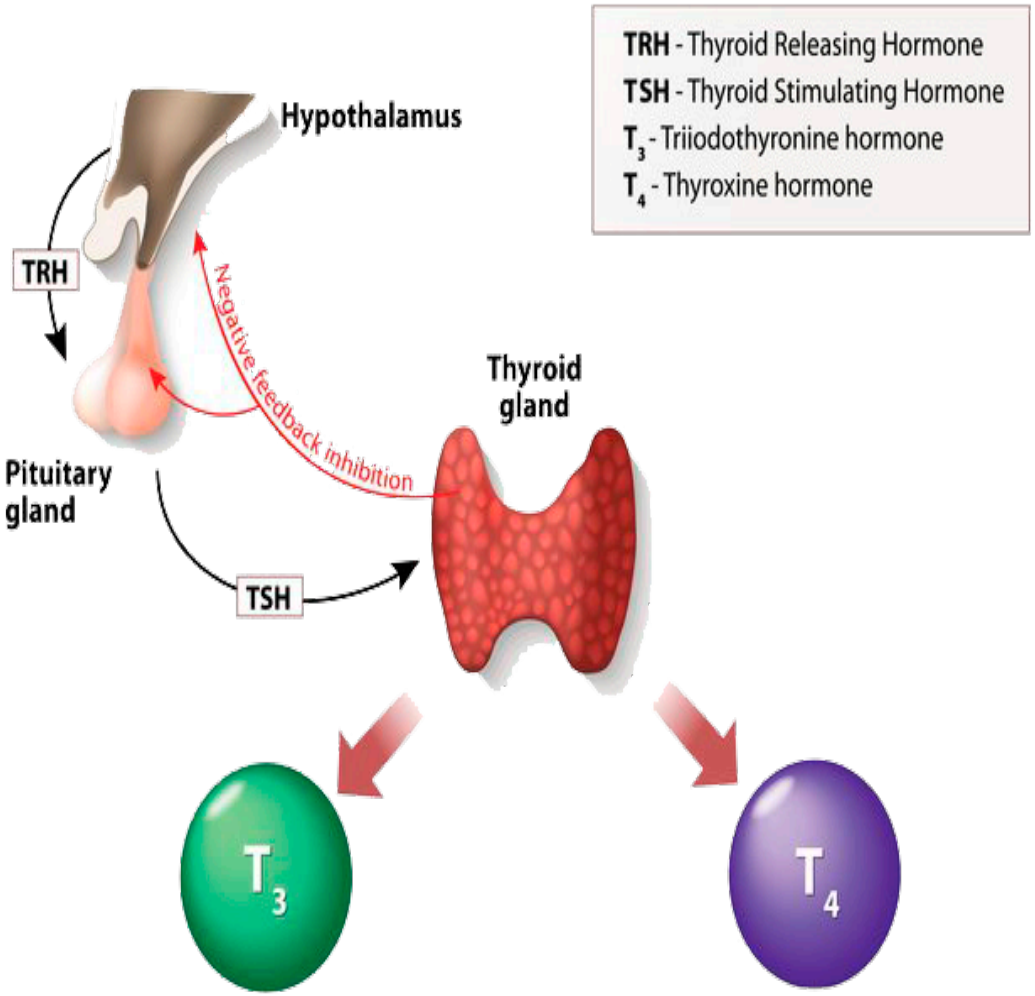
Garber (2012). Clinical Practice Guidelines for Hypothyroidism in Adults: AACE & ATA 2012.

Why is TSH not the best indicator?

- TSH inversely correlated with pituitary T3 levels
  - With physiologic stress, depression, IR, DM, aging, calorie deprivation, inflammation, chronic fatigue, etc…increasing pituitary T3 levels are associated with diminished CELLULAR and tissue T3 levels and increased reverse T3
- TSH may NOT correlate with cellular levels of thyroid hormone
- Pituitary has unique composition of deiodinases not present in any other tissue in the body
  - Pituitary T3, and thus TSH, is poor indicator for tissue T3 in the rest of the body
- Pituitary T3 and TSH levels remained unchanged in response to chronic inflammation and illness, while T3 levels in the peripheral tissues are significantly reduced

HPT Axis

- Thyroxine (T4) 92%
- Triiodothyronine (T3) 8%
- T1, T2, Calcitonin



Zoeller RT, Tan SW, Tyl RW. General background on the hypothalamic-pituitary-thyroid (HPT) axis. Crit Rev Toxicol 2007;37 (1-2):11-53

Bianco AC, Salvatore D, Gereben B, Berry MJ, Larsen PR. Biochemistry, cellular, and molecular biology, and physiological roles of the iodothyronine selenodeiodinases. Endocrine Reviews 2002;23(1):38-39

Functions of Thyroid Hormones

Regulate

- Temperature
- Metabolism
  - Increase fat breakdown resulting in weight loss as well as lower cholesterol.
  - Help fix leptin resistance (increased hunger, slowed metabolism)
- Cerebral Function
- Energy

Protect Against

- Cardiovascular Disease
- Cognitive Impairment
- Fatigue & Weight Gain
- Memory Loss

Cabanelas A, Lisboa PC, Moura EG, Pazos-Moura CC. Leptin acute modulation of the 5'-deiodinase activities in hypothalamus, pituitary and brown adipose tissue of fed rats. *Horm Metab Res* 2006;38(8):481-5

Krotkiewski M. Thyroid hormone and treatment of obesity. *Int J Obes Relat Metab Disorder* 2000;24(2):S116-S119

Araujo RL, Andrade BM, da Silva ML, et al. Tissue-specific deiodinase regulation during food restriction and low replacement dose of leptin in rats. *Am J Physiol Endocrinol Metab* 2009;296:E1157-E1163

Deiodinases

- Enzymes that serve as essential control points of thyroid activity
- Determine intracellular activation and deactivation of thyroid hormones independent of serum hormone levels
- 3 distinct deiodinases present in different tissues of the body
  - D1 (converts T4 to T3)
  - D2 (converts T4 to T3)
  - D3 (converts T4 to reverse T3)
- D1 works in the liver and kidney
- D2 is the key enzyme that controls intracellular T3

Bianco, AC, Salvatore D; 2002: Biochemistry, cellular and molecular biology, and physiologic roles of the iodothyronine selenodeiodinases. *Endocrine Reviews* ; 23 (1):38-39

Deiodinases

- D1 and D2 are downregulated and suppressed by the following:
  - Physiologic and emotional stress, Depression, Dieting
  - Insulin Resistance, Obesity, Diabetes
  - Inflammation (AI disease, systemic illness)
  - Chronic Fatigue Syndrome, Chronic Pain
  - EXPOSURE TO TOXINS

Mebis, L, et al. Type II iodothyronine is up-regulated in skeletal muscle in critical illness. *J Endocr Metab* 2007; 92(8):3330-3333.

Jackson I. The thyroid axis and depression. *Thyroid* 1998;8(10):951-956

Araujo RL, et al. Tissue-specific deiodinase regulation during food restriction and low replacement dose of leptin in rats. *Am J Phys Endoc Metab* 2009;296:E1157-E1163

Islam S, et al. A comparative study of thyroid hormone levels in diabetic and non-diabetic patients. *SE Asian J Trop Med Public Health* 2008;39(5):913-916

Lowe JC, et al. Effectiveness and safety of T3 for euthyroid fibromyalgia. *Clin Bull Myofascial Ther* 1997;2(2/3):31-58

Moriyama K, et al. Thyroid hormone action is disrupted by bisphenol A as an antagonist. *J Clin Endocrin Metab* 2002;87(11):5185-5190

Low Triiodothyronine (T3)

Verga SB, Donatelli M, et al. A low reported energy intake is associated with metabolic syndrome. *J Endocrinology Invest* 2009;32:538-541

Wallace DC. A mitochondrial paradigm of metabolic and degenerative diseases, aging, and cancer: a dawn for evolutionary medicine. *Ann Rev Genetics* 2005;39(1):359-407

Park JH, Niermann KJ, et al. Evidence for metabolic abnormalities in the muscles of patients with fibromyalgia. *Curr Rheumatology Rep* 2000;2(2): 131-140

Escobar-Morreale HF, et al. Replacement therapy for hypothyroidism with thyroxine alone does not ensure euthyroidism in all tissues, as studied in thyroidectomized rats. *J Clin Invest* 1995;96(6): 2828-2838

Samuels MH, Schuff KG, et al. Health status, psychological symptoms, mood, and cognition in L-thyroxine treated hypothyroid subjects. *Thyroid* 2007;17 (3):249-58

Cooke RG, Joffe RT, et al. T3 augmentation of antidepressant treatment in T4-replaced thyroid patients *J Clin Psychiatry* 1992;53(1):16-8

It is the low T3 at the cell level that is responsible for the symptoms

- Not TSH
- Not T4

Signs/Symptoms

- OVER 200 symptoms are related to thyroid deficiency:
- Weak, Cold, Tired, Fatigued
- Thin Hair, Thin Skin, Thin Nails
- Weight Gain, Increased Body Fat
- Loss of Energy & Motivation
- Loss of Cognition, Memory, Mood
- Poor Sense of Well-Being, Depression
- Infertility, Loss of Libido, Menstrual Irregularities
- Constipation/compromised gut motility

Harrison's Principles of Internal Medicine, 20th edition

Hypothyroidism

30-40% of Americans are hypothyroid =

52 MILLION PEOPLE

Type 2 Hypothyroidism, by Mark Starr MD

Reasons for Thyroid Deficiency

Larsen PR. Thyroid-pituitary interaction: feedback regulation of thyrotropin secretion by thyroid hormones. NEJM 1982;306(1):23-32
Maia AL, et al. Pituitary cells respond to thyroid hormone by discrete, gene-specific pathways. Endocrinology 1995;136:1488-1494
Ortiga-Carvalho TM, et al. Thyroid hormone receptors and resistance to thyroid hormone disorders. Nat Rev Endocrinology 2014;10(10):582-591

Decreased production by the gland

Decreased conversion of T4 to T3

Less effectiveness at the receptor sites causing low thyroid symptoms in spite of “normal” blood levels

Types of Hypothyroidism

- **Primary Hypothyroidism**
  - Decreased Production of Thyroid Hormones
  - TSH elevates, T3 and T4 will be normal or low depending on severity
- **Secondary Hypothyroidism**
  - Poor conversion of T4 to T3 in peripheral tissue
  - Conversion of T4 to reverse T3 (rT3)
  - Euthyroid sick syndrome = Low T3 Syndrome
- **Tertiary Hypothyroidism**
  - Receptor site insensitivity
  - Symptoms of low thyroid persist despite normal labs

Harrison's Principles of Internal Medicine, 20th edition
Persani L. Jour of Clin Endocrin and Metabol. 2012; 9(7): 3068-3078

Causes of decreased production

- Autoimmune thyroiditis
- Surgical removal of the gland
- Iodine deficiency
- Failure of the hypothalamus or pituitary gland
- Inflammatory cytokines involved in the stress response
- Gastrointestinal lipopolysaccharides, an endotoxin produced from bacterial overgrowth aka Leaky Gut

Secondary & Tertiary Hypothyroidism

- **Secondary**
  - Same symptoms as primary hypothyroidism
  - Same Low T3 as primary hypothyroidism
  - TSH normal in Low T3 Syndrome
  - Problem is in conversion of T4 to T3, not production of T4
  - Decreased conversion secondary to stress, illness, fasting, age
- **Tertiary**
  - Improvement occurs only with thyroid replacement in spite of normal levels

Lab Values

FREE T3 2.3 – 4.3 (lab range)

- OPTIMAL 4.0 – 4.3

TSH 0.3 – 5.0 (lab range)

- New proposed TSH levels .3 – 2.0
- OPTIMAL .3

Treatment Options

- Levothyroxine/Synthroid/Tirosint (T4)
- Cytomel/liothyronine (T3)
- Desiccated Thyroid (T4/T3/T1/T2)
- Non-Desiccated Compounded (T4/T3)

Synthetic Levothyroxine

- Contains no T3
- Mild efficacy in converting into T3
- Many brands & generic available (may result in daily fluctuations due to FDA acceptance of up to 30% tolerance in fluctuation
- Tirosint has no dyes but is expensive
- Can use with Cytomel (liothyronine), if needed, in patients who cannot tolerate or do not do well on premixed desiccated
- Sometimes may be used in Hashimoto's patients along with T3 (liothyronine)

Desiccated Thyroid

- T4 and T3 and T1 and T2
- Porcine not bovine
- Compounded synthetic T4 & T3 (non-desiccated) can be used for religious purposes
- Desiccated is premixed at fixed (9 µg T3 & 38 µg T4) concentration
  - cannot be changed as it is pre-blended together before distribution
- NP Thyroid more readily available & well-absorbed
  - Doses in tablets in grains or milligrams

1/4	1/2	1	2	3	grain
15	30	60	120	180	mg

Non-Dessicated, Compounded T4 & T3

- Not premixed as is desiccated thyroid
- Can combine in any concentration
- T4 is mixed with T3 by the pharmacist to any combination that is requested
- Not porcine; useful for religious preferences
- $$

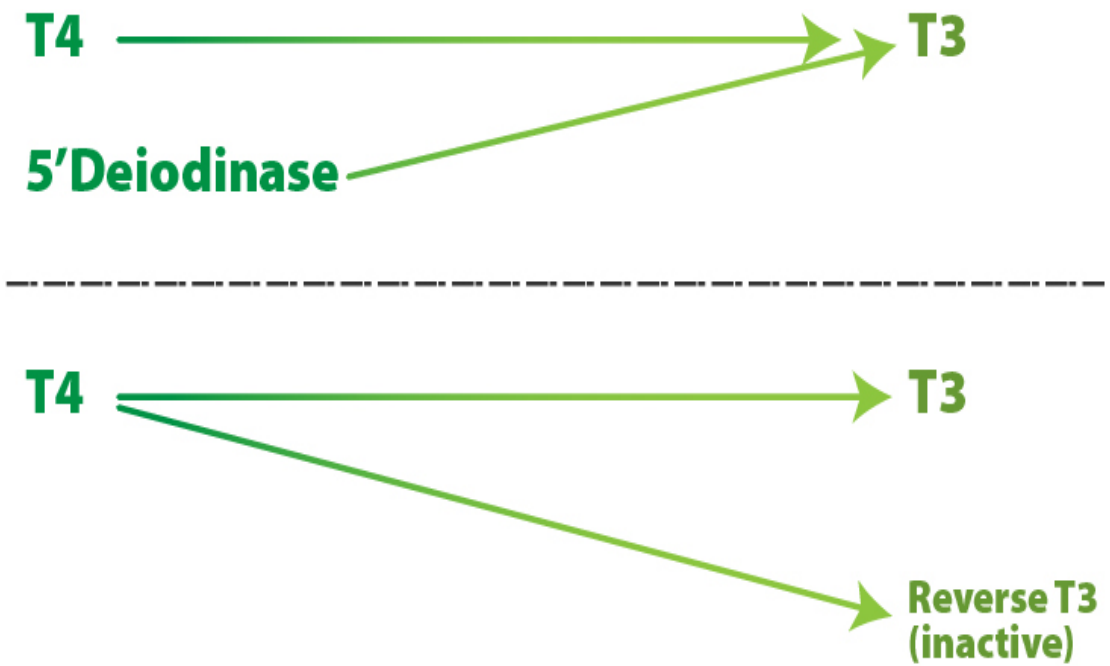
Recommended Treatment: T4 & T3

- Raising T3 levels to optimal will improve symptoms
- Raising T3 levels cannot be accomplished with just T4 alone
- Combination of T4 & T3 is required in order to optimize T3
- Desiccated thyroid is treatment of choice

J Clin Endocrin Metabolism, Hoang TD et al. Desiccated Thyroid Extract Compared With Levothyroxine in the Treatment of Hypothyroidism: A Randomized, Double-Blind, Crossover Study; 2013

Journal of Endocrinology, Diabetes, and Obesity, Pepper GM et al. Conversion to Armour Thyroid from Levothyroxine Improved Patient Satisfaction in the Treatment of Hypothyroidism; 2014

T4 is converted to T3 in periphery - normally



T4 easily crosses BBB; T3 does not
Brain has very adequate supply of 5'Deiodinase; body does not.

BOTH T4 & T3 ARE NEEDED

Recommendations for Screening

ACOG in a recent *PAUSE* Magazine stated "the thyroid can affect many of your bodily functions and is an important regulator of your metabolism….you should get it checked starting at age 50 and every 5 years thereafter"

→

Same recommendations as American College of Physicians…

Indications for Treatment

- Low T3 levels
- Symptoms of thyroid insufficiency
- Elevated TSH
- Prevention of cardiovascular disease
- Optimizing health
- Optimizing well-being
- Memory
- Healthy metabolism

Arguments for Combo T3/T4

- Patients prefer it
- T3 is needed for adequate tissue levels of thyroid
- D1 is expressed in the liver, kidney, lung, pituitary & thyroid, D2 is expressed in CNS, heart doesn't have D activity and needs T3
- IR/DM/Metabolic Syndrome/Obesity cause a significant reduction in T4 to T3 conversion, an intracellular deficiency in T3, and an increased conversion of T4 into rT3
- One study found that in 70 obese patients with "normal" standard thyroid function tests treated with T3 20 mcg daily ONLY for 6 weeks there was a clinically significant reduction in CV risk factors… lipids, markers for IR

Danzi. Potential uses of T3 in the treatment of human disease. Clin Cornerstone. 2005
Katzeff HL, Selgrad C. Impaired peripheral thyroid metabolism in genetic obesity. *Endocrinology* 1993;132(3): 989-995
Islam S, et al. A comparative study of thyroid hormone levels in diabetic and non-diabetic patients. *SE Asian J Trop Med Public Health* 2008;39(5):913-916
Krotkiewski M. Thyroid hormone and treatment of obesity. *Int J Obes Relat Metab Disorder* 2000;24(2):S116-S119

T4 only preparations are not appropriate in conditions associated with reduced mitochondrial function or ATP production

- Includes IR, DM, obesity, depression, anxiety, chronic fatigue, fibromyalgia, migraines, infections, CVD, inflammation
- Small decreases in cellular ATP concentration resulted in major reductions in the transport of T4 and only barely affected T3 uptake
- The above conditions (along with high cholesterol, fatty acids or trigs) inhibits T4 transport into the cell (not T3).

Hennemann, RD, Friesema E, et al.(2001). Plasma Membrane Transport of Thyroid Hormones and Its Role in Thyroid Hormone Metabolism and Bioavailability. *Endocrine Reviews*,22, 451–476.

Levothyroxine versus NDT

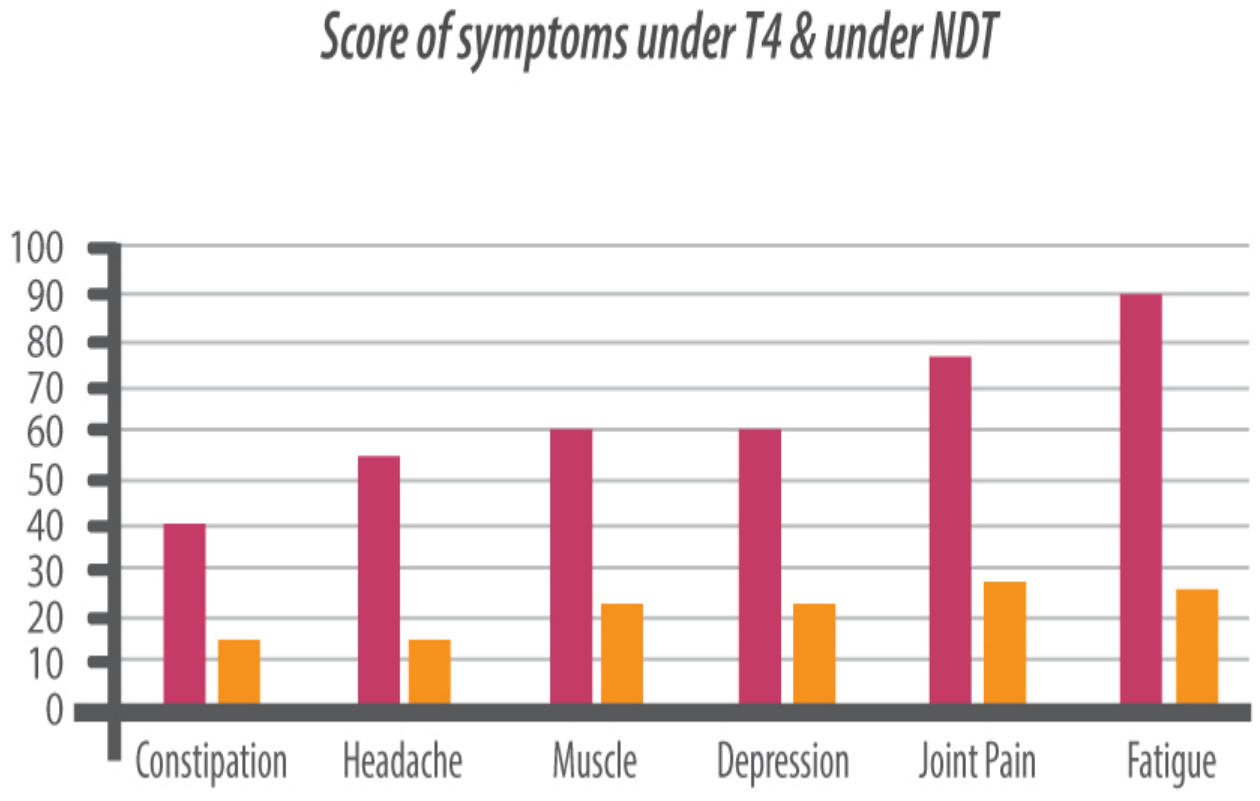
- Patients prefer NDT
- Weight loss with NDT
- Respondents taking DTE less likely to report problems with weight management, fatigue/ energy levels, mood, and memory compared to those taking LT4 or LT4 + LT3
- AT treatment was preferred over LT4 replacement therapy by 78% of patients with hypothyroidism in the sub-group with persistent subjective complaints while on T4-only therapy. No serious adverse events were noted while on AT treatment **including 30 subjects aged 65 yrs or older.**
- Patients report to be dissatisfied with their providers and treatment when on LT4

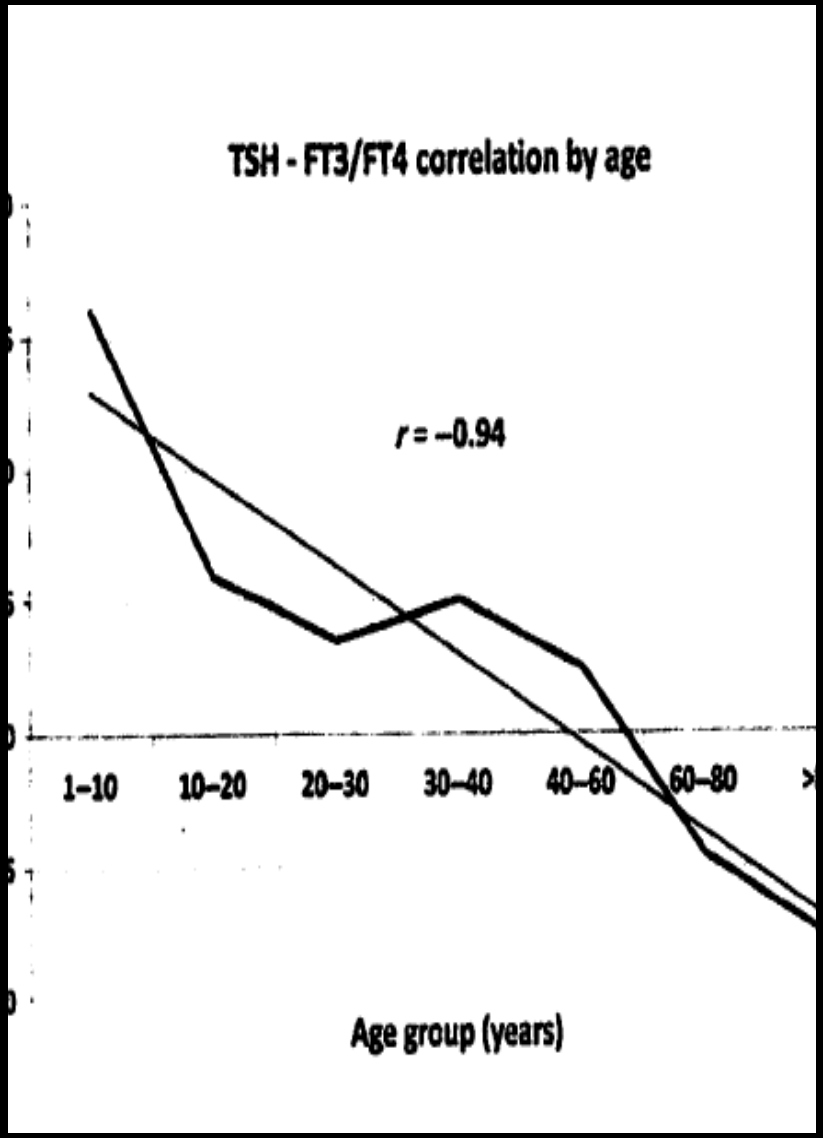
Hoang TD et al, Desiccated Thyroid Extract Compared With Levothyroxine in the Treatment of Hypothyroidism: A Randomized, Double-Blind, Crossover Study. *J Clin Endocrin Metabolism*, 2013

Journal of Endocrinology, Diabetes, and Obesity, Pepper GM et al. Conversion to Armour Thyroid from Levothyroxine Improved Patient Satisfaction in the Treatment of Hypothyroidism; 2014

Thyroid, Peterson SJ et al. An Online Survey of Hypothyroid Patients Demonstrates Prominent Dissatisfaction; 2018

Synthetic vs. NDT





Can You Convert T4 to T3 as You Age?

EJE 2016;175:49-54

Transitioning T4 to DTE

Alternate between T4 and DTE for 2 weeks

Be sure to start on the correct DTE dose (relative to their labs and current T4 dosage)

Use the conversion chart

Dosing/Adjustment

- ¼ grain, ½ grain, 1 grain, 2 grains, 3 grains

- Initiate with ½ to 1 grain dose typically
- Increase by 1/4 to 1/2 grain increments per month as tolerated

- Monitor lab tests and symptoms monthly (use your discretion here) until optimal

- Ensure correct dose and timing (consider BID dosing)
- Ensure compliance
- Every AM on empty stomach (not as important with DTE)
- Draw blood 5 hours after taking the AM dose (VERY IMPORTANT)

Monitoring

- **Optimize the labs & the symptoms, NOT T4 or TSH**
  - Free T3 (4.0-4.3)

- **TSH vs Free T3**
  - Free T3 is active hormone at the cellular level and at mRNA
  - TSH and T4 are not active hormones in spite of the fact that they are the most commonly utilized lab tests
  - TSH & T4 are only accurate tests of pituitary thyroid levels, NOT cellular levels

Symptomatic Improvements vs. TSH Suppression?

- ACOG Recommendation: The reason for treating with menopausal hormones is to improve **symptoms**
- AACE states treat the **TSH value**, not the patient or symptom
- Recommendation: **Treat the symptoms and not the lab tests**

What to do?

Side Effects

- Sweating
- Palpitations
- Tachycardia
- Tremor or nervousness
- **Rarely** seen with standard doses and normal free T4 & free T3
- Excess vs. sensitivity
  - Treatment → lower dose
  - ?Divided doses?

Thyroid & Disease Processes

- Osteoporosis
- Heart Disease/CHF/ Arrythmias
- Inflammation
- Stroke
- Dementia

If the patient is asymptomatic, why do we care about treating their deficiency?

- T3 is needed for fat loss, & 40% of Americans are obese
- T3 protects against arrhythmias and heart disease
- T3 decreases with stress or dieting, prolonged hypothyroidism results in elevated cortisol levels resulting in further decreased conversion on T4 to T3 and increases amounts of rT3
- Increased risk for anemia and other immunologic changes with low thyroid

DOES THYROID REPLACEMENT CAUSE OSTEOPOROSIS?

Studies say NO!!

Studies showing no increase in osteoporosis

- Low thyrotropin levels are not associated with bone loss in older women: a prospective study. J Clin Endocrinol Metab. 1997 Sep;82(9):2931-6.
- Lack of deleterious effect on bone mineral density of long-term thyroxine suppressive therapy for differentiated thyroid carcinoma. Endocr Relat Cancer. 2005 Dec;12(4):973-81
- Randomized trial of pamidronate in patients with thyroid cancer: bone density is not reduced by suppressive doses of thyroxine, but is increased by cyclic intravenous pamidronate. J Clin Endocrinol Metab. 1998 Jul;83(7):2324-30
- Hip bone mineral density, bone turnover and risk of fracture in patients on long-term suppressive L-thyroxine therapy for differentiated thyroid carcinoma. Eur J Endocrinol. 2005 Jul;153(1):23-29.
- Thyroid hormone use and the risk of hip fracture in women >/=65 years: a case-control study. J Womens Health (Larchmt). 2003 Jan-Feb;12(1):27-31.
- Treatment of benign nodular goiter with mildly suppressive doses of L-thyroxine: effects on bone mineral density and on nodule size. J Intern Med. 2002 May;251(5):407-414.
- Subclinical thyroid dysfunction and hip fracture and bone mineral density in older adults: the cardiovascular health study J Clin Endocrinol Metab. 2014 Aug;99(8):2657-64
- Bone mineral density in well-differentiated thyroid cancer patients treated with suppressive thyroxine: A systematic overview of the literature. J Surg Oncol. 2002 Jan;79(1):62-70.
- Levothyroxine treatment and occurrence of fracture of the hip. Arch Intern Med. 2002 Feb 11;162(3):338-43.

Does thyroid replacement increase the risk of heart disease and/or arrhythmias?

The opposite is actually true

How does low thyroid lead to heart disease/arrythmias?

- Mucin accumulation
- Increased incidence of inflammation and infection
- Diastolic hypertension
- Swelling, dyspnea
- Bradycardia, PVCs and A Fib
- V Tach is associated with Low T3, low ratio of T3/T4 and high reverse T3 (Shimoyama, 1993)

Heart Disease, CHF, Arrythmias

- Low T3 is associated with adverse outcomes in patients with ACS undergoing PCI
- Low T3 is related to increased early and late mortality in NSTE-ACS patients
- Low T3 is not uncommon in patients suffering from an acute coronary event
- Low T3 predicts worse hospital outcomes in patients with acute HF and can be useful in the risk stratification of these patients.
- LT3S was associated with more severe myocardial injury and increased in-hospital CV mortality in patients with AMI

Long-term outcome in patients with heart failure treated with levothyroxine

- Retrospective Danish cohort study with 224,670 patients diagnosed with HF
  - 6560 treated with L-T4 at baseline
  - 9007 initiated L-T4 at a follow up

- Context
  - Hypothyroidism detrimental on CV system
  - Controversy concerning benefits of L-T4 (levothyroxine) substitution in patients with HF

Einfeldt MN, Olsen AS, et al., *J Clin Endocrinology Metab,* 2019;104(5):1725-1734

Long-term outcome in patients with heart failure treated with levothyroxine

- Follow-up
  - Mean follow-up of 4.8 years
- Conclusion
  - Ongoing and incident L-T4 associated with increased risk and all-cause mortality, CV death, and MACE
  - Increased risk MI for ongoing treatment
  - Reduced risk observed for incident treatment

Einfeldt MN, Olsen AS, et al., *J Clin Endocrinology Metab,* 2019;104(5):1725-1734

Strokes

- Low FT3 value upon admission is associated with a poor 3-month functional outcome and mortality in patients with acute stroke
- Low T3 syndrome in the acute phase of ischemic stroke was associated with a higher prevalence of 1-month post stroke cognitive impairments independently of established risk factors
- Low T3 syndrome in acute stroke patients is an effective prognostic factor for predicting greater baseline stroke severity, poorer functional outcome, and higher overall mortality risk.

Suda S, et al. *J **Stroke** Cerebrovasc Dis.* 2018 Oct;27(10):2804-2809. Low Free Triiodothyronine Predicts 3-Month Poor Outcome After Acute Stroke.
Chen H, et al. *Am J Geriatr Psychiatry.* 2018 Jul 29. Low Tri-iodothyronine Syndrome is Associated With Cognitive Impairment in Patients With Acute Ischemic Stroke: A Prospective Cohort Study.
Lamba N, Liu C, et al. *Clin Neurol Neurosurg.* 2018 Jun;169:55-63. A prognostic role for Low tri-iodothyronine syndrome in acute stroke patients: A systematic review and meta analysis.

Heart Disease References

1. Cao Q, et al. *Cardiol J*. 2018 Sep 20. Association between mild thyroid dysfunction and clinical outcome in acute coronary syndrome undergoing percutaneous coronary intervention.
2. Yazıcı S et al. *J Clin Lab Anal*. (2017). Relation of Low T3 to One-Year Mortality in Non-ST Elevation Acute Coronary Syndrome Patients.
3. Lamprou V, et al. *Clin Cardiol*. 2017 Aug;40(8):528-533. The role of thyroid hormones in acute coronary syndromes: Prognostic value of alterations in thyroid hormones.
4. Rothberger GD, Gadhvi S, et al. *Am J Cardiol*. 2017 Feb 15;119(4):599-603. Usefulness of Serum Triiodothyronine (T3) to Predict Outcomes in Patients Hospitalized With Acute Heart Failure.
5. Su W, Zhao XQ, et al. *J Cardiol*. 2018 Sep;72(3):215-219. Low T3 syndrome improves risk prediction of in-hospital cardiovascular death in patients with acute myocardial infarction.
6. Chang X, Zhang S, Zhang M, et al. *Lipids Health Dis*. 2018 Oct 12;17(1):234. Free triiodothyronine and global registry of acute coronary events risk score on predicting long-term major adverse cardiac events in STEMI patients undergoing primary PCI.

Dr. Broda Barnes

- In 1970, 1,569 patients on natural thyroid hormone who were observed for a total of 8,824 patient years.
- Classified by age, sex, elevated cholesterol, and high blood pressure, and compared to similar patients in the Framingham Study.
- Based on the statistics derived in the Framingham Study, 72 of Dr. Barnes's patients should have died from heart attacks; however, only four patients had done so.
- This represents a decreased heart attack death rate of 95% in patients who received natural thyroid hormone

Importance of Tx Type II Hypothyroidism

Table 3.3 Comparison of the Framingham Study Prediction of Coronary Cases versus Dr. Barnes' Actual Cases Observed among His Patients.

TABLE 3.3

Sex	Classification	# of Patients Treated	Patient Years	Study Coronary Prediction	Barnes' Actual Cases
F	Age 30-59	490	2,705	7.6	0
F	High Risk**	172	1,086	7.3	0
F	Age Over 60	182	955	7.8	0
M	Age 30-59	382	2,192	12.8	1
M	High Risk**	186	1,070	18.5	2
M	Age Over 60	157	816	18.0	1
	TOTALS	1,569	8,824	72.0	4

***HIGH RISK = HIGH CHOLESTEROL, HIGH BLOOD PRESSURE, OR BOTH*

OVER 90% OF PREDICTED HEART ATTACKS FROM THE FARMINGHAM STUDY WERE PREVENTED.

Source: Barnes, B. Hypothyroidism, the Unsuspected Illness, Harper and Row, 1976. Page 180. Reprinted with permission.

Inflammation

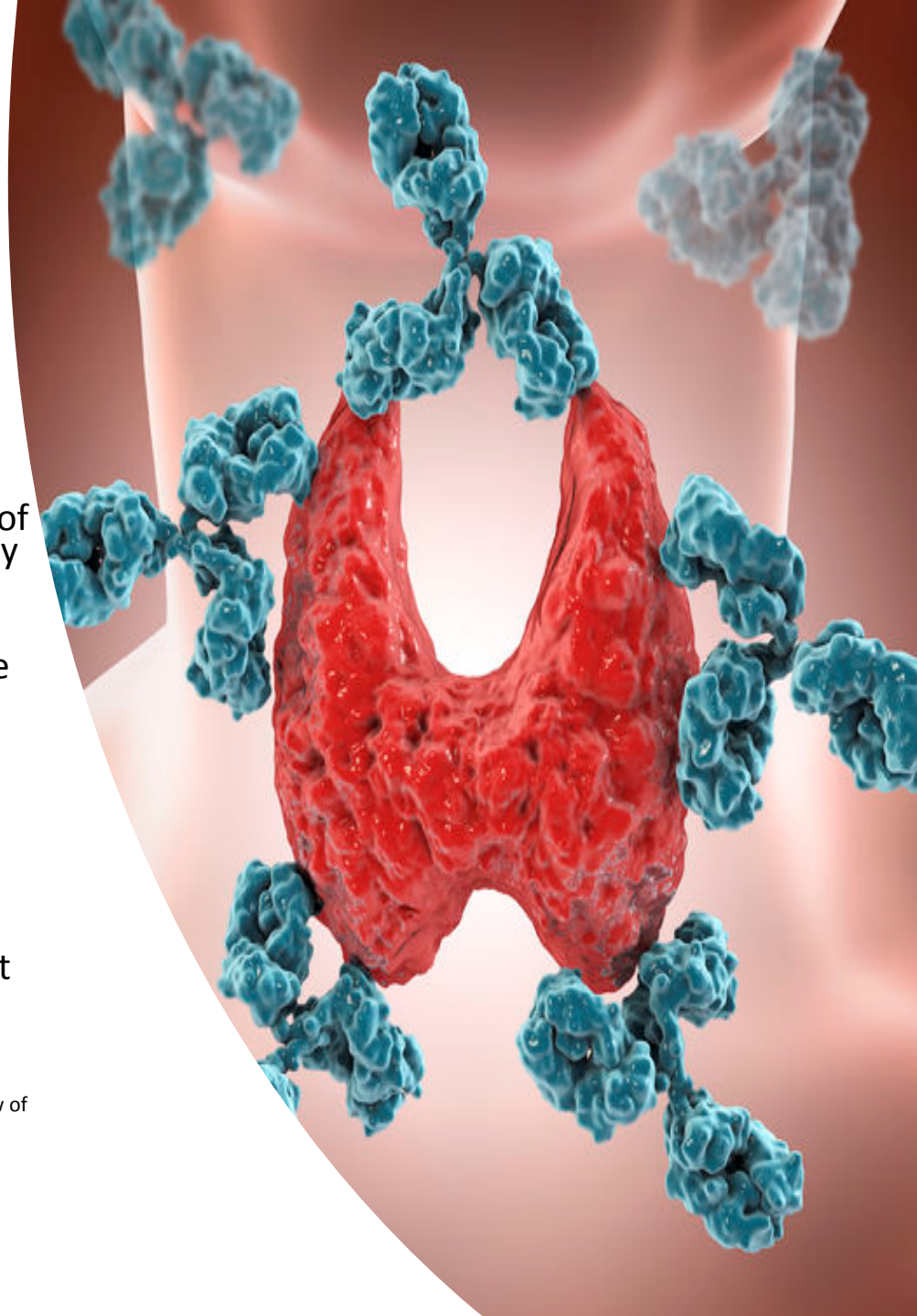
- Thyroid Hormone Lowers CRP- Christ-Crain, 2003
- Lowers Homocysteine- Nedrebo, 1998
- IL-6 is positively correlated with rT3 and negatively correlated with Free T3- Boelen 1993

Alzheimer's

- Higher serum FT3 is associated with lower risk of conversion to AD.
- Patients in the lowest serum FT3 quartile had a twofold increased risk of AD compared to those in the highest quartile
- Inverse, linear association between serum FT3 and risk of ADK

Quinlan P, Horvath A, et al. Psychoneuroendocrinology. 2018 Sep 5;99:112-119. Low serum concentration of free triiodothyronine (FT3) is associated with increased risk of Alzheimer's disease.

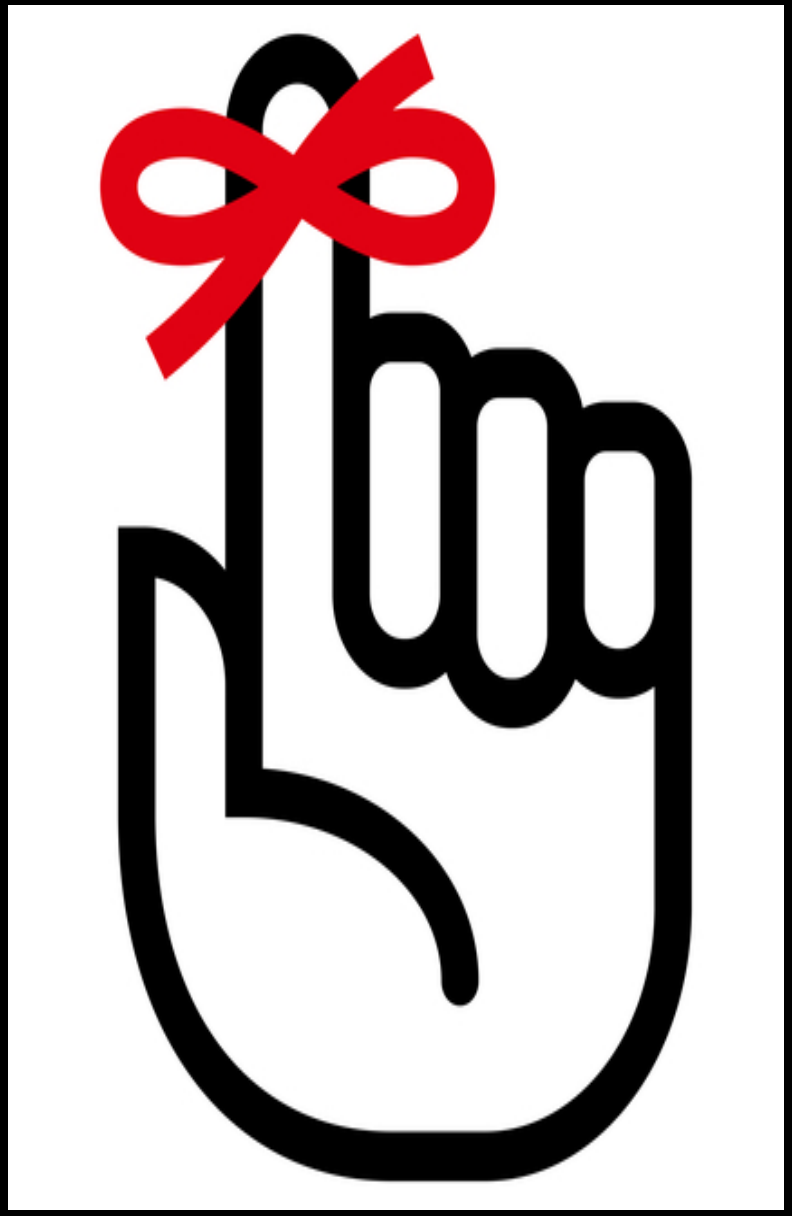
Hashimoto's Thyroiditis



- Autoimmune disease, most common cause of thyroid illness in U.S., incidence rising rapidly
- Often occurs between ages 30-50, more common in women (8:1)
- 20% of patients have hypothyroid SX at time of DX
- Positive anti-TPO AND/OR Thyroglobulin antibodies (Tg)
- Exists concomitantly with other AI diseases (RA, SLE, Sjogren's, Celiac, etc)
- Could be a genetic component
- Onset might be triggered by environment (iodine status, toxins, heavy metals, nutrient deficiencies, food intolerances, stress, etc)

McLeod DS, et al. The incidence and prevalence of thyroid autoimmunity. *Endocrine*. 2012;42:252-265

McGrogan A, et al. The incidence of autoimmune thyroid disease: a systematic review of the literature. *Clin Endocrinology (Oxf)*. 2008;69:687-96



Hashimoto's Treatment

- Treat with NP Thyroid
- Treat non-responders with Synthroid 0.1 mg daily (or Tirosint) and Cytomel 5 mcg BID
- Iodine ---in US, iodine levels have fallen 50% over last 30 years
  - Hashimoto's thyroiditis has been increasing
  - If antibodies increase on iodine, STOP the iodine (in some pts, antibodies decrease on iodine; in some increases)
- Address nutrient deficiencies
- Gluten-free diet
- Gut health very important

Iron Deficient Sub-Clinical Hypothyroidism

- Is it the chicken or the egg?
- Randomized, Double Blind, Controlled Study
- When both iron def anemia and hypothyroidism coexist, oral iron therapy will be ineffective
- Increases in Hgb, RBC mass, and serum ferritin was statistically greater in the iron/ levothyroxine group
- If you do not correct the anemia, there may be an intolerance to thyroid hormone

J Clin Endocrinol Metab January 2009;94:151-56
Mayo Clic Proceedings. 200; 75: 189-192

Iodine and TSH

Does iodine cause TSH to raise? **YES**

Does this mean the thyroid gland is failing? **NO**

Iodine is transported into the cell by a transport molecule, sodium-iodide symporter (NIS)

NIS is stimulated by TSH

When iodine supplements are started, you will see TSH elevate as the body produces more symporters to move iodine into the cell

Transient phenomenon

Newer References

Heart disease, CHF, CM, Arrythmias

Cao Q, et al. *Cardiol J*. 2018 Sep 20. Association between mild thyroid dysfunction and clinical outcome in acute coronary syndrome undergoing percutaneous coronary intervention.

"Mild thyroid dysfunction was frequent in patients with ACS undergoing PCI. Low T3 syndrome was the predominant feature and was associated with 12-month adverse outcomes in these patients."

Yazıcı S et al. *J Clin Lab Anal.* (2017). Relation of Low T3 to One-Year Mortality in Non-ST Elevation Acute Coronary Syndrome Patients.

"Low T3 is related to increased early and late mortality in NSTE-ACS patients. Free T3 levels may be used to identify NSTE-ACS patients with high mortality risk."

Lamprou V, et al. *Clin Cardiol.* 2017 Aug;40(8):528-533. The role of thyroid hormones in acute coronary syndromes: Prognostic value of alterations in thyroid hormones.

"Alterations in thyroid hormone plasma concentrations, especially low triiodothyronine (T3) levels, represent a hormonal imbalance that is not uncommon among patients suffering an acute coronary event. Although further large-scale clinical trials are needed, the low T3 syndrome manifesting in patients during ACS might be useful in prognostic stratification."

Heart disease, CHF, CM, Arrythmias

Rothberger GD, Gadhvi S, et al. *Am J Cardiol*. 2017 Feb 15;119(4):599-603. Usefulness of Serum Triiodothyronine (T3) to Predict Outcomes in Patients Hospitalized With Acute Heart Failure.

"In conclusion, low T_3 predicts worse hospital outcomes in patients with acute HF and can be useful in the risk stratification of these patients."

Su W, Zhao XQ, et al. *J Cardiol.* 2018 Sep;72(3):215-219. Low T3 syndrome improves risk prediction of in-hospital cardiovascular death in patients with acute myocardial infarction.

"LT3S was associated with more severe myocardial injury and increased in-hospital CV mortality in patients with AMI. Furthermore, it improved risk prediction of in-hospital CV death post-AMI when it was added to the TIMI risk score."

Chang X, Zhang S, Zhang M, et al. *Lipids Health Dis.* 2018 Oct 12;17(1):234. Free triiodothyronine and global registry of acute coronary events risk score on predicting long-term major adverse cardiac events in STEMI patients undergoing primary PCI.

"The low FT3 level, a common phenomenon, is a strong predictor of long-term poor prognosis in STEMI patients undergoing PCI."

Strokes

Suda S, et al. *J **Stroke** Cerebrovasc Dis.* 2018 Oct;27(10):2804-2809. Low Free Triiodothyronine Predicts 3-Month Poor Outcome After Acute Stroke.

"Our data suggest that a low FT3 value upon admission is associated with a poor 3-month functional outcome and mortality in patients with acute stroke."

Chen H, et al. *Am J Geriatr Psychiatry.* 2018 Jul 29. Low Tri-iodothyronine Syndrome is Associated With Cognitive Impairment in Patients With Acute Ischemic Stroke: A Prospective Cohort Study.

"Low T3 syndrome in the acute phase of ischemic stroke was associated with a higher prevalence of 1-month PSCI, independently of established risk factors".

Lamba N, Liu C, et al. *Clin Neurol Neurosurg.* 2018 Jun;169:55-63. A prognostic role for Low tri-iodothyronine syndrome in acute stroke patients: A systematic review and meta analysis.

"Low-T3 syndrome in acute stroke patients is an effective prognostic factor for predicting greater baseline stroke severity, poorer functional outcome, and higher overall mortality risk."

Cancer

Gao R, Chen RZ, Xia Y, et al. *Int J Cancer.* 2018 Aug 1;143(3):466-477. Low T3 syndrome as a predictor of poor prognosis in chronic lymphocytic leukemia.

"Serum FT3 level was positively related to protein metabolism and anemia, and inversely related to inflammatory state…. Low T3 syndrome may be a good candidate for predicting prognosis in future clinical practice of CLL."

Larisch R, Midgley JEM, et al. *Exp Clin Endocrinol Diabetes.* 2018 Sep;126(9): 546-552. Symptomatic Relief is Related to Serum Free Triiodothyronine Concentrations during Follow-up in Levothyroxine-Treated Patients with Differentiated Thyroid Cancer.

"Residual hypothyroid complaints in LT4-treated patients are specifically related to low FT3 concentrations. This supports an important role of FT3 for clinical decision making on dose adequacy.."

Gao R et al. *Br J Haematol.* (2017). Low T3 syndrome is a strong prognostic predictor in diffuse large B cell lymphoma.

Cancer

Sasson M, Kay-Rivest E, et al. *J Otolaryngol Head Neck Surg.* 2017 Apr 4;46(1):28. The T4/T3 quotient as a risk factor for differentiated thyroid cancer: a case control study

"…a direct relationship between high levels of fT4 and malignancy was uncovered. Furthermore, low levels of TSH and fT4 increased the likelihood that a nodule was benign. In this study a fT4/fT3 ratio >3.3 increased the risk of malignancy by 3.6 times" (**HIGH T4 INACTIVATING DEIODINASES PERHAPS??)**

Bunevicius A, Deltuva VP, et al. Preoperative low tri-iodothyronine concentration is associated with worse health status and shorter five year survival of primary brain tumor patients. *Oncotarget.* 2017 Jan 31;8(5):8648-8656.

"The Low tri-iodothyronine syndrome is common in brain tumor patients and is associated with poor functional and cognitive status, and with worse discharge outcomes. The Low tri-iodothyronine syndrome is associated with shorter survival of glioma patients."

Cancer

Action of Reverse T3 on Cancer Cells

In the present studies, we show that rT3 caused increases in proliferation in vitro of 50-80% ($p<0.05$-0.001) of human breast cancer and glioblastoma cells.

"rT3 may be a host factor supporting cancer growth."

Endocr Res. 2019 Apr 3:1-5. doi: 10.1080/07435800.2019.1600536. [Epub ahead of print]

Breast CA

Ortega-Olvera C, et al. ***Breast Cancer*** *Res.* 2018 Aug 9;20(1):94. Thyroid hormones and breast cancer association according to menopausal status and body mass index.

"Higher serum total T4 (TT4) concentrations were associated with BC in both premenopausal and postmenopausal women. Lower TT3 concentrations were associated with BC in both premenopausal and postmenopausal women…"

Wu CC, Yu YY, Yang HC, et al. *Arch Gynecol Obstet.* 2018 Aug;298(2):389-396. Levothyroxine use and the risk of breast cancer: a nation-wide population-based case-control study.

"The results of the present study are the first to suggest that levothyroxine use increased the risk of breast cancer…..a larger long-term prospective randomized-controlled trial specifically designed to assess the effect of levothyroxine use on the risk of developing breast cancer is needed."

Alzheimer's/Parkinson's Disease

Quinlan P, Horvath A, et al. *Psychoneuroendocrinology*. 2018 Sep 5;99:112-119. Low serum concentration of free triiodothyronine (FT3) is associated with increased risk of Alzheimer's disease.

"Higher serum FT3 was associated with lower risk of conversion to AD. Furthermore, patients in the lowest serum FT3 quartile had a twofold increased risk of AD compared to those in the highest quartile….in a memory clinic population, there was an inverse, linear association between serum FT3 and risk of AD…"

Choi SM, Kim BC, et al. *Dement Geriatr Cogn Disord.* 2014;38(3-4):178-85. Thyroid status and cognitive function in euthyroid patients with early Parkinson's disease.

"This study supports a relationship between the thyroid status and cognitive function in euthyroid early PD patients, with higher concentrations of fT4 being associated with a poor performance of executive function."

Alzheimer's/Q.O.L.

Cognitive functioning and quality of life in patients with Hashimoto thyroiditis on long-term levothyroxine replacement

- 130 Patients Age 20-49 and >50 y.o. on T4 with HT
- Conclusion: Patients on long-term levothyroxine replacement show persistent impairments in both cognitive functioning and general well-being.

Thyroid Function in Patients with Type 2 Diabetes Mellitus and Diabetic Nephropathy: A Single Center Study

Patients with DN had higher TSH levels and lower FT3 levels than those without DN ($p<0.01$). The prevalence of SCH and low FT3 syndrome in patients with DN was 10.8% and 20.9% respectively, higher than that of controls and patients without DN ($p<0.05$). Through Pearson correlation or Spearman rank correlation analysis, in patients with DN, there were positive correlations in TSH with serum Cr ($r=0.363, p=0.013$) and urinary albumin-to-creatinine ratio ($r=0.337, p=0.004$), and in FT3 with eGFR with statistical significance ($r=0.560, p<0.001$).

"High level of TSH and low level of FT3 were observed in T2DM patients with DN. Routine monitoring of thyroid function in patients with DN is necessary, and management of thyroid dysfunction may be a potential therapeutic strategy of DN"

J Thyroid Res. 2018 Dec 2;2018:9507028. doi 10.1155/2018/8507028. eCollection 2018


T hank You