Diagnosis and Treatment of Hypothyroidism in Challenging Cases

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Disclosure Statement

I do not have any financial arrangements, or affiliations with any commercial entities whose products, research or services may be discussed in these materials.

I am the owner of Holtraceutical supplements.

Lecture Goals

Concepts:

- Understand why thyroid resistance is the most common form of hypothyroidism (low cellular thyroid activity despite normal TFT's)
- Understand the limitations of TSH and other thyroid function tests, especially with chronic illness
- To learn the causes of thyroid resistance, how to recognize it and how to treat
- To learn why standard T4 therapy is inadequate for most patients
- To understand the importance of local control of cellular thyroid levels (deidodinase activity and cellular thyroid transport)

Case Study #1

- 42 y/o women comes in complaining of inability to lose weight, ongoing depression on antidepressants, fatigue and muscle pain. She has been diagnosis with fibromyalgia, bipolar depression and type II diabetes.
- She is on metformin, an SSRI, hydrocodone for pain and Lipitor. She has tried numerous antidepressants and Lyrica without benefit.
- She brings in labs showing a TSH of 1.2, free T4 of 1.7 (0.8-1.8) and a free T3 of 2.6 (2.3-4.2).

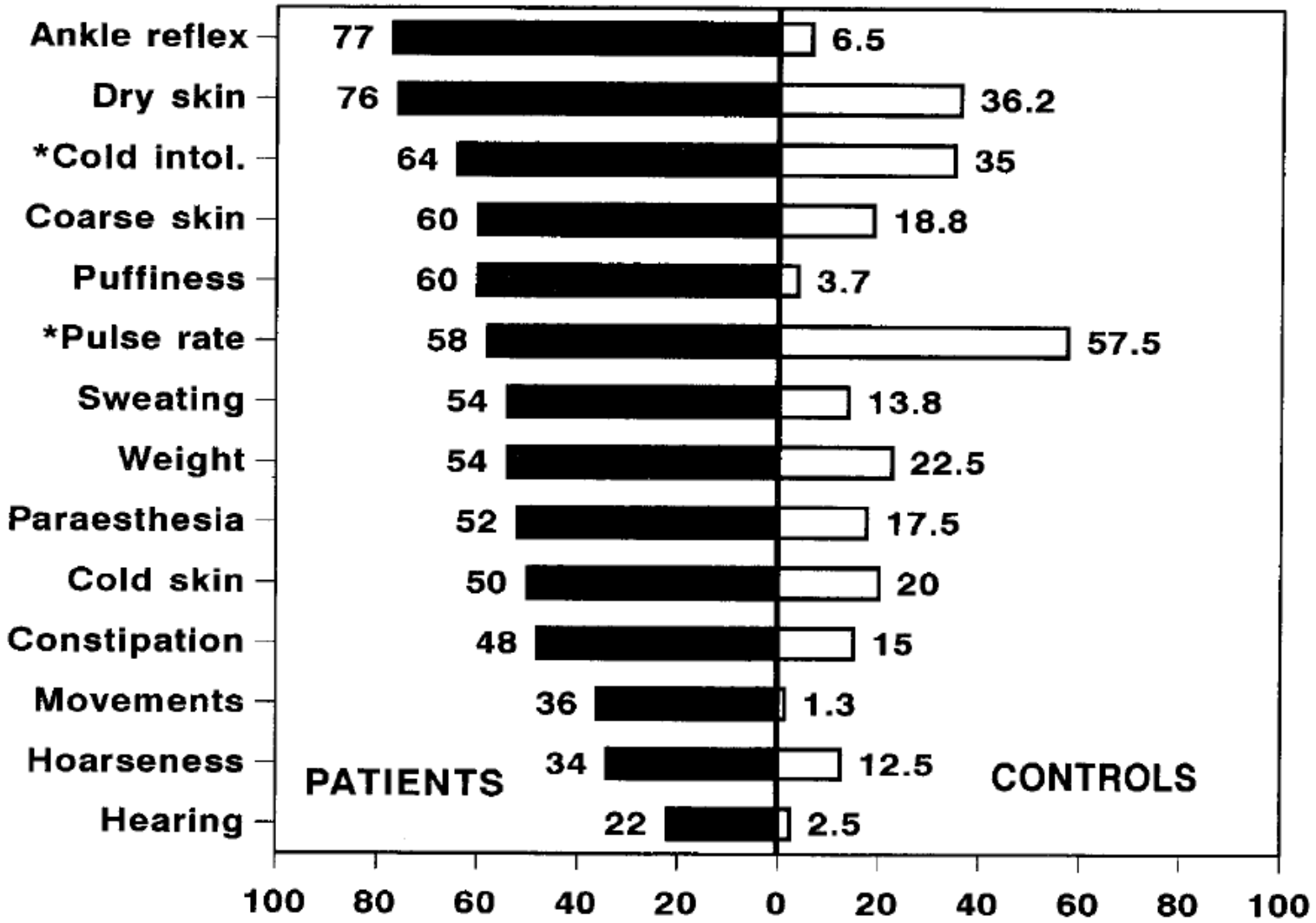
Diagnosis of Low Thyroid

- What is the chance this patient has low thyroid levels contributing to her symptoms?
- What can be done to further evaluate her thyroid function?

Symptoms of low thyroid

- Fatigue
- Depression
- Weight gain/difficulty losing weight
- Cold extremities
- Dry or coarse skin
- Constipation
- Cold intolerance
- Hair loss or dry hair
- Poor memory
- Poor concentration
- Anxiety
- Lack of sweating
- Weakness
- Pale skin
- Shortness of breath
- PMS
- Heavy menstrual flow
- Muscle or joint aches
- Poor motivation
- Water retention
- Migraines

Frequency of hypothyroid symptoms and signs (in %) in patients (n=50) and controls (n=80)



Clinical Score: Evaluation of Patients with Various Grades of Hypothyroidism and Controls JCEM 1997;82(3):3 771-776

ESTIMATION OF TISSUE HYPOTHYROIDISM

TABLE 1. Sensitivity and specificity of the 14 symptoms and signs of hypothyroidism and analysis of their positive and negative predictive values

Symptoms and signs	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Ankle reflex	77	93.5	92.2	80.3
Dry skin	76	63.8	67.7	72.7
Cold intolerance[a]	64	65	64.6	64.4
Coarse skin	60	81.2	76.1	67
Puffiness	60	96.3	94.2	70.7
Pulse rate[a]	58	42.5	50.2	50.3
Sweating	54	86.2	79.6	65.2
Wt increase	54	77.5	70.6	62.8
Paraesthesia	52	82.5	74.8	63.2
Cold skin	50	80	71.4	61.5
Constipation	48	85	76.2	62
Slow movements	36	98.7	96.5	60.7
Hoarseness	34	87.5	73.1	57
Hearing	22	97.5	89.8	52.6

Zulewski H, et al. Estimation of Tissue Hypothyroidism by a New Clinical Score: Evaluation of Patients with Various Grades of Hypothyroidism and Controls JCEM 1997;82(3):3 771-776

Diagnosis-signs/symptoms

You can use this sheet to track your progress with your symptoms by rating them before, during and after treatment (marking the dates at the top of each column). You can rate each symptom on a scale of 1 to 10 on how you feel; 10 being how you imagine a normal person to feel, 1 being terrible.

PUT DATES HERE:	before	during	after		before	during	after
Fatigue				Abnormal throat sensations			
Headaches				Sweating abnormalities			
Migraines				Heat and/or cold intolerance			
PMS				Low self esteem			
Irritability				Irregular periods			
Fluid retention				Sever menstrual cramps			
Anxiety				Low blood pressure			
Panic attacks				Frequent colds and sore throats			
Hair loss				Frequent urinary infections			
Depression				Light-headedness			
Decreased Memory				Ringing in the ears			
Decreased concentration				Slow wound healing			
Decreased sex drive				Easy bruising			
Unhealthy nails				Acid indigestion			
Low motivation				Flushing			
Constipation				Frequent yeast infections			
Irritable Bowel Syndrome				Cold hands/feet, turn blue?			
Inappropriate weight gain				Poor coordination			
Dry skin				Increased nicotine/caffeine use			
Dry hair				Infertility			
Insomnia				Hypoglycemia			
Needing sleep during the day				Increased skin infections/Acne			
Arthritis and joint aches				Abnormal swallowing sensations			
Allergies				Changes in skin pigmentation			
Asthma				Prematurely grey/white hair			
Muscular Aches				Excessively tired after eating			
Itchiness of skin				Carpal Tunnel Syndrome			
Elevated cholesterol				Dry eyes/blurred vision			
Ulcers				Hives			
				Bad breath			
				TOTAL FOR BOTH SIDES (out of 600)			

Do you have or feel the following symptoms?	No Symptom Never	Few or Sometimes	Moderate or regularly	Much or Often	Always or Extreme
Sensitive to cold	☐	☐	☐	☐	☐
Cold hands or feet	☐	☐	☐	☐	☐
Generalized fatigue	☐	☐	☐	☐	☐
Morning fatigue	☐	☐	☐	☐	☐
Fatigue unless exercising	☐	☐	☐	☐	☐
Sleepy during day	☐	☐	☐	☐	☐
Distracted easily	☐	☐	☐	☐	☐
Poor motivation for required tasks	☐	☐	☐	☐	☐
Depression	☐	☐	☐	☐	☐
Headaches	☐	☐	☐	☐	☐
Water retention	☐	☐	☐	☐	☐
Constant swollen eyelids	☐	☐	☐	☐	☐
Swollen eyes in morning	☐	☐	☐	☐	☐
Swollen calves/feet	☐	☐	☐	☐	☐
Difficulty losing weight despite dieting	☐	☐	☐	☐	☐
Constipation	☐	☐	☐	☐	☐
Bedwetting as child	☐	☐	☐	☐	☐
Slow heart palpitations	☐	☐	☐	☐	☐
Muscle cramps	☐	☐	☐	☐	☐
Carpal tunnel syndrome	☐	☐	☐	☐	☐
Stiff joints in morning	☐	☐	☐	☐	☐
Joint pain worsens with cold	☐	☐	☐	☐	☐
Hoarse voice in morning	☐	☐	☐	☐	☐
Dry skin (general/feet or elbows)	☐	☐	☐	☐	☐
Slow growing or brittle nails	☐	☐	☐	☐	☐
Diffuse hair loss	☐	☐	☐	☐	☐
Muscle achiness or soreness	☐	☐	☐	☐	☐
Low body temperature	☐	☐	☐	☐	☐
Diminished sweating	☐	☐	☐	☐	☐
Tingling or numbness in extremities	☐	☐	☐	☐	☐
Hoarse voice (constant or in morning)	☐	☐	☐	☐	☐
Decreased hearing	☐	☐	☐	☐	☐
Course skin (rough skin)	☐	☐	☐	☐	☐

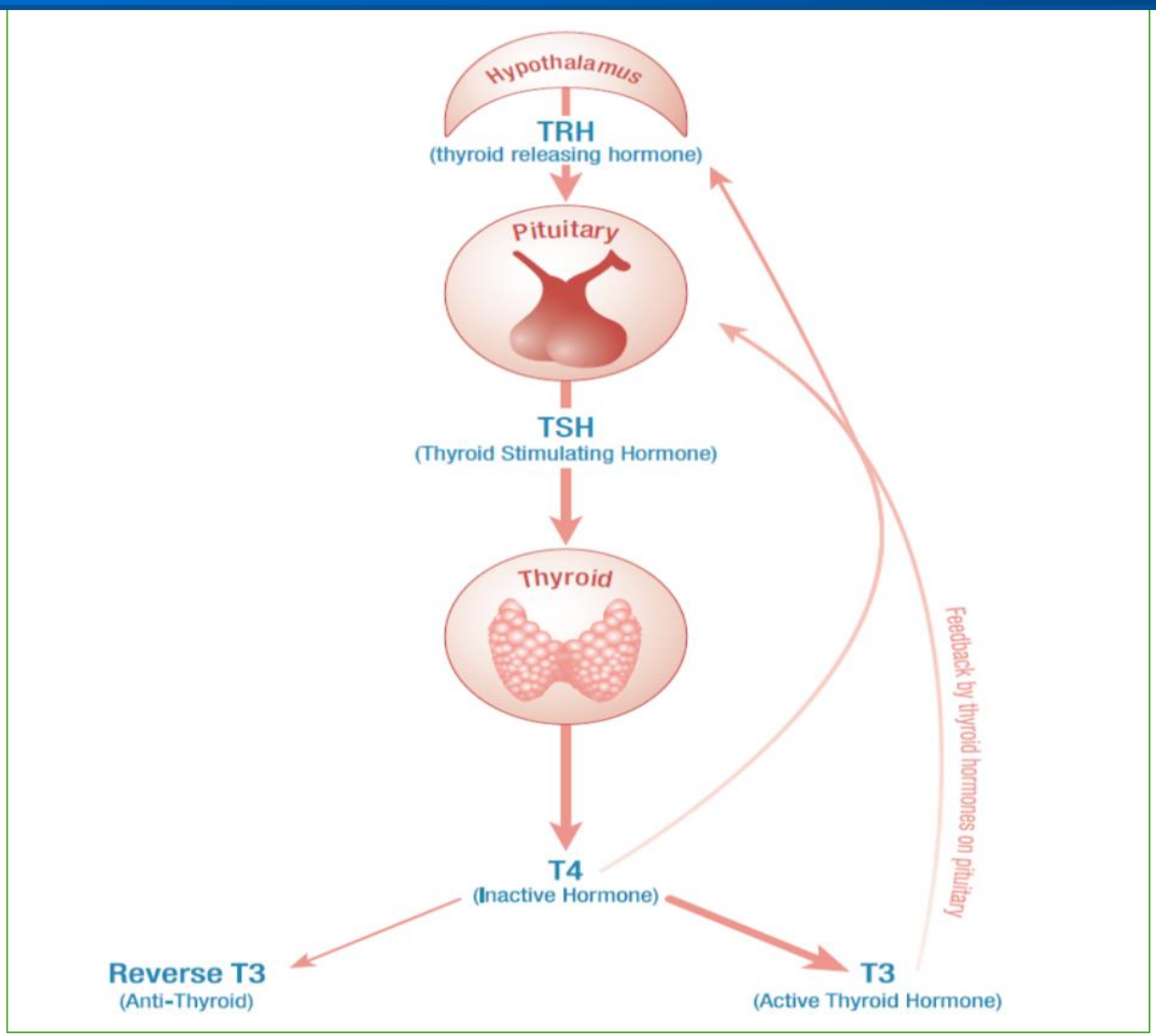
Required steps to have thyroid activity

- Hypothalamic/pituitary function common
- Secretion of TSH common
- Thyroid function (secretion of T4) not common
- Thyroid hormone transport into cell common
- Conversion of T4 to T3 common
- Receptor binding common
- Downstream activation unknown
-
- Are the abnormalities/dysfunctions present common or uncommon?

Thyroid Resistance

- General term--Thyroid in blood has less effect
- Can be secondary to reduced T4 to T3 conversion, reduced transport, receptor blockage (toxin, genetics or infection), coagulation defect or reduced post-binding translation
- Can remove resistance by removing causative agent (toxin, infection, inflammation, physiologic stress, glucose dysregulation, depression, weight and diet issues, pain, etc.)
- Overcome by increasing levels of thyroid replacement
- Clinical diagnosis but blood tests can support

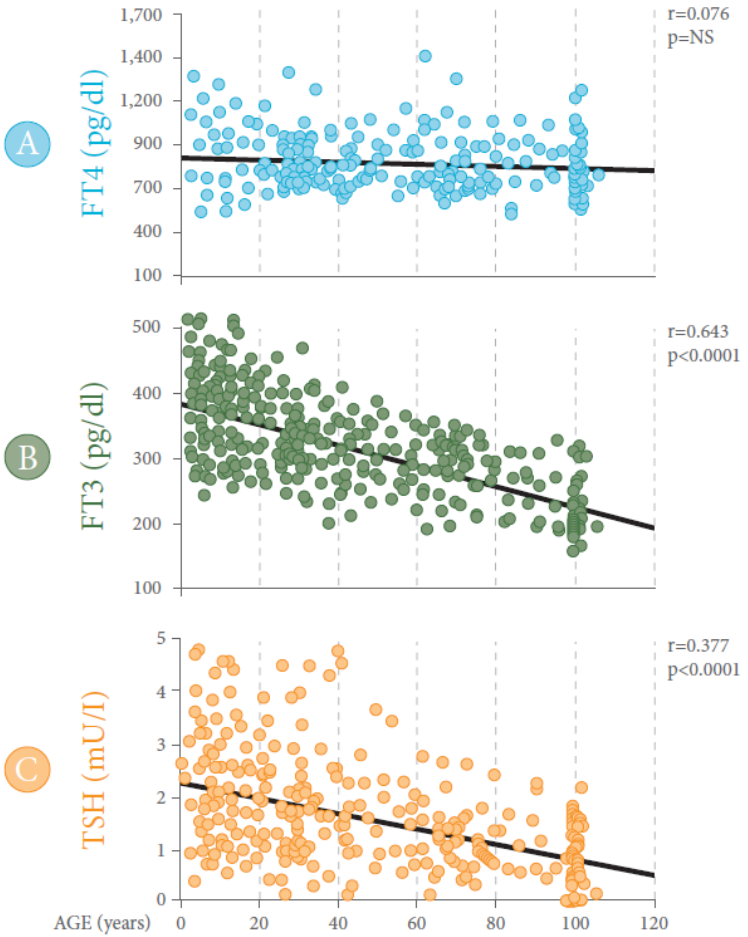
Thyroid Physiology
(without physiologic stress)



Diagnosis of Low Thyroid

- Standard (traditional) way to diagnose low thyroid is based on elevation of TSH above 4.2-5.7 (depending on lab)
- This method misses over 80% of people of low thyroid, especially with chronic illness
- Many patients complain of numerous symptoms of low thyroid but 90% of doctors will not treat with thyroid because they focus on a normal TSH

Age dependent variations in mean serum levels of Free T4 (A), Free T3 (B) and TSH (C) in healthy individuals-a combined analysis of the literature. Demonstrates that TSH is not a reliable marker of active thyroid (T3) levels (low T3 levels are associated with decreased, not increased, TSH levels).



1. Schwartz E, Holtorf, K. Hormones in Wellness and Disease Prevention: Common Practices, Current State of the Evidence, and Questions for the Future. Prim Care Clin Office Pract 2008;35:669–705
2. Mariotti S, Barbesino G, Caturegli P, et al. Complex alteration of thyroid function in healthy centenarians. J Clin Endocrinol Met 1993;77(5):1132.
3. Verheecke, P. Free triiodothyronine concentration in serum of 1050 euthyroid children is inversely related to their age. Clin Chem 1997;43(6): 963-967.
4. Quest Diagnostics assay validation free T3, free T4 and TSH, San Juan Capistrano, CA
5. Jankowska H. The effect of age on parameters of thyroid function. Endokrynol Pol. 1993;44(2):117-27.

Pituitary

KEY TO UNDERSTANDING THYROID

- The pituitary is different than every other tissue in the body:
  - Different deioidinases in pituitary than peripheral tissues
  - Different thyroid transporters (discussed in detail at Lyme lecture)
  - Different high sensitivity receptors
  - The pituitary does not become thyroid resistant
  - T3 level in pituitary have inverse correlation to T3 levels in peripheral tissues in the presence of chronic illness

Thyroid Resistance

- Studies show that with any sickness, inflammation or physiological stress there is a decrease in TSH, T4, T3 and an increase in RT3 due to a suppression and down-regulation of D1 and an activation of D2 and D3.
- There is reduced T3 and T3 transport into the tissues (T4 more affected than T3)
- The more severe the illness or stress, the more severe the intracellular T3 deficiency, while TSH does not elevate because pituitary is different than every other tissue in the body

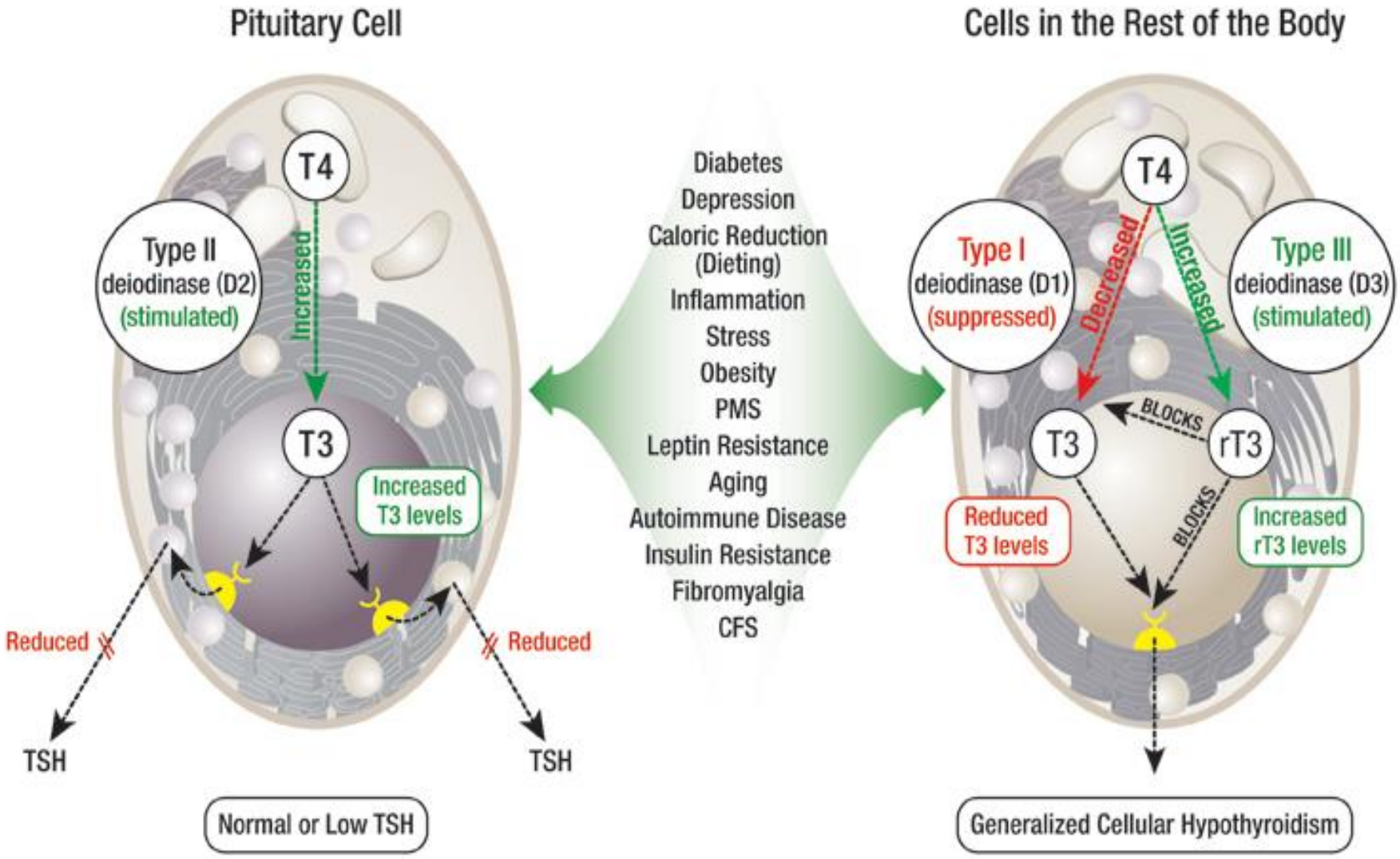
Holtorf, K. Understanding Local Control of Thyroid Hormones: (Deiodinases Function and Activity. J Restor Med 2014;3(1):1-52

Thyroid Resistance

- Shown to occur with response to physiologic and emotional stress;[11-22] depression;[23-45] dieting; [46-51] weight gain and leptin resistance;[47-91] insulin resistance, obesity and diabetes;[91-99] inflammation from autoimmune disease or systemic illness;[11,100,102-115] chronic fatigue syndrome and fibromyalgia;[121-125] chronic pain;[116-120] and exposure to toxins, pesticides and plastics.[126-134]
- In the presences of such conditions there are reduced tissue levels of active thyroid in all tissues except the pituitary

Holtorf, K. Thyroid Hormone Transport into Cellular Tissue J Restor Med 2014;3(1):53-68

Why the TSH is Unreliable



Accuracy of TSH in Fibromyalgia

- TRH testing of FM patients
- Found that **all** of the patients with fibromyalgia were hypothyroid despite the fact that standard thyroid function tests, including TSH, T4 and T3, were in the normal range.
- They found that these patients tended to have low normal TSH levels that averaged 0.86 vs. 1.42 in normals with high normal free T4 and low normal T3 levels so doctors erroneously feel these patients are on the high side of normal because of the low normal TSH and high normal T4.

Neeck G, Riedel W. Thyroid function in patients with fibromyalgia syndrome. J Rheum 1992;19(7):1120-1122

Accuracy of TSH in chronic fatigue

- A study published in *The Lancet* performed thyroid biopsies in patients with chronic fatigue and found that 40% of these patients had lymphocytic thyroiditis.
- Only 40% of those with lymphocytic thyroiditis were positive for TPO or antithyroglobulin antibodies or had an abnormal TSH.
- Thus, the thyroid dysfunction would have gone undetected in the majority of patients if the biopsy had not been done.
- This study also demonstrated that because the TSH is a poor indicator of thyroid function, it also does not predict whose symptoms will respond to thyroid replacement.
- The authors state, "*After treatment with thyroxine, clinical response was favorable, irrespective of baseline TSH concentration.*"

Wikland B. Fine needle aspiration cytology of the thyroid in chronic fatigue. *Lancet* 2001:357:956-57.
Wikland B, *et al*. Subchemical hypothyroidism. *Lancet* 2003;361:1305.

Accuracy of TSH with PMS

- A study published in the *New England Journal of Medicine* investigated the incidence of hypothyroidism in women with PMS using TRH testing
- Found that 94% of patients with PMS had thyroid dysfunction (tissue hypothyroidism) compared to 0% of the asymptomatic patients.
- 65% of the hypothyroid patients had thyroid tests in "normal" range and could only be diagnosed by TRH testing (missed by the usual thyroid function tests).
- They found that all PMS patients had significant improvement in symptoms with thyroid treatment even though the standard blood tests were "normal."

Gold MS et al. Hypothyroidism and depression. JAMA 1981;245(19):1919-1922.

Accuracy of TSH with PMS

- Found 70% of women with PMS had abnormal TRH testing, showing thyroid dysfunction despite having normal TSH levels

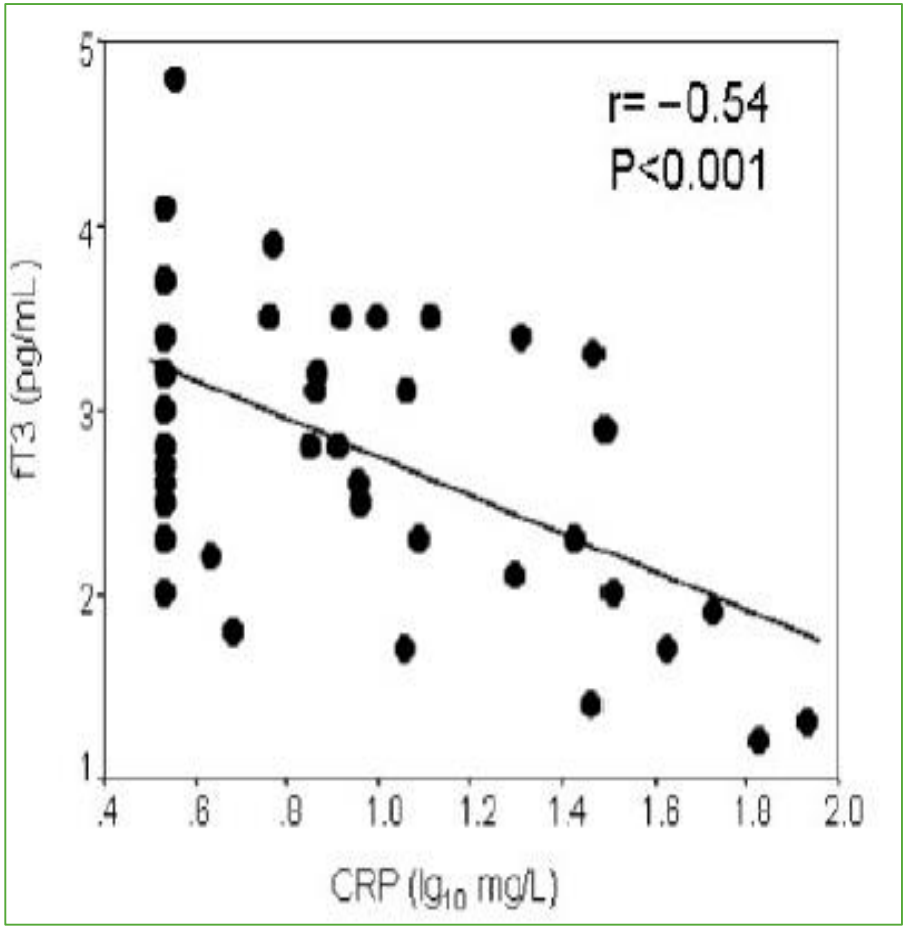
Roy-Byrne PP, et al. TSH and prolactin responses to TRH in patients with premenstrual syndrome. Am J Psychiatry 1987;144(4):480-484.

Accuracy of TSH with Obesity

- A study in the *Journal of Endocrinology and Metabolism* examined the accuracy of using the TSH to identify hypothyroidism in obese individuals via TRH testing
- The study found that while the TSH levels were not significantly different between normal weight and obese individuals…
- 36% of obese patients had severe thyroid dysfunction not detected by standard TSH testing

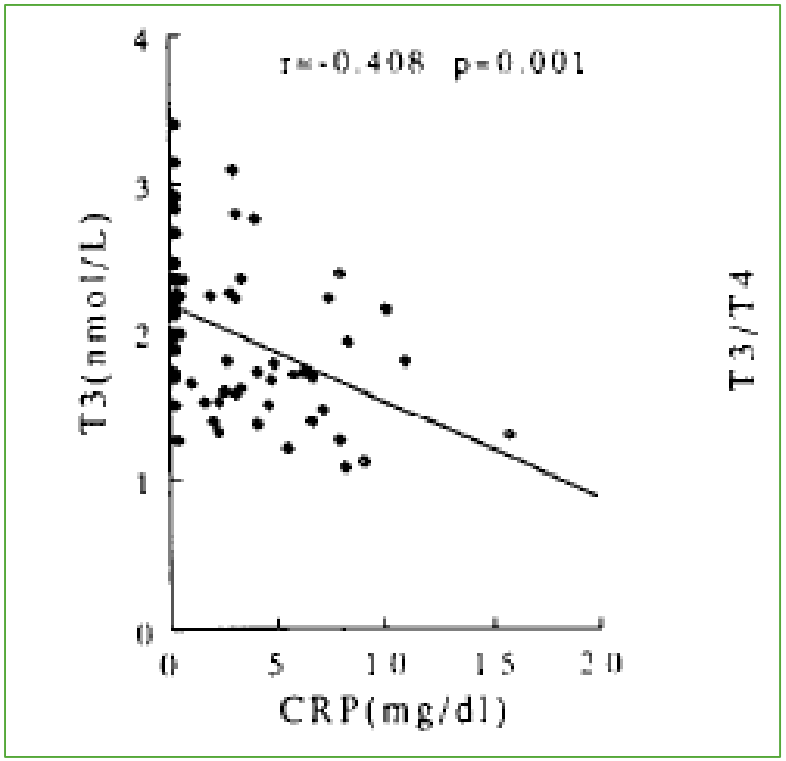
Donders S H. Disparity of thyrotropin (TSH) and TSH-releasing hormone in obesity. JCEM;1985;61(1):56-9.

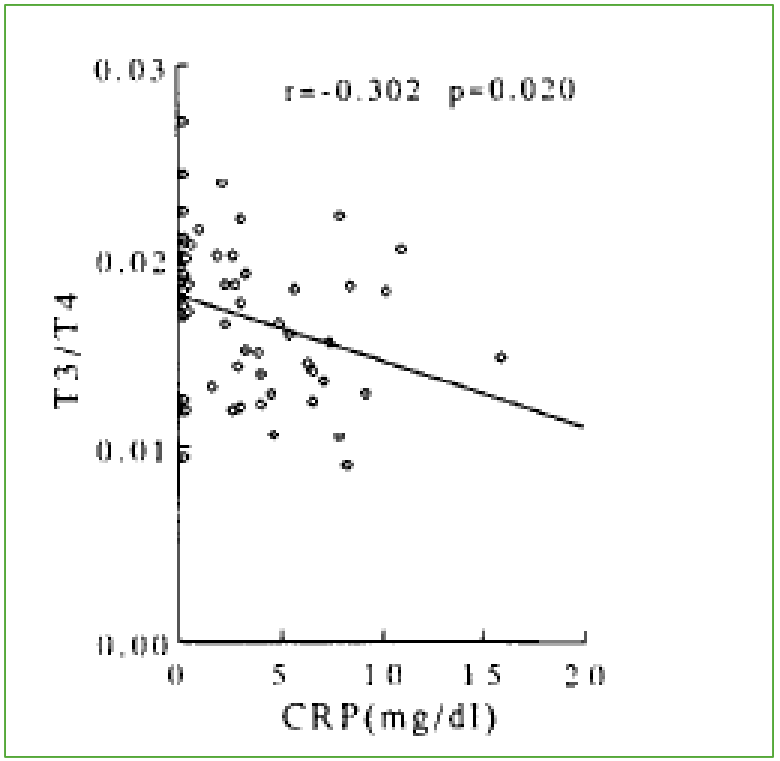
Inflammation



Enia G et al. Subclinical hypothyroidism is linked to micro-inflammation and predicts death in continuous ambulatory peritoneal dialysis. Nephrol Dial Transplant (2007) 22: 538–544

Inflammation





Hashimoto H et al. Serum I-l 6 and thyroid hormone in children J Clin Endocrinol Metab. 1994 Feb;78(2):288-91.

Reverse T3 (competitive inhibitor of T3)

- Reverse T3 is thought to be an inactive metabolite…
- But clearly demonstrated to be a competitive inhibitor of T3 (blocks T3 at the receptor)

Res Exp Med (Berl) 1997;197(4):211-7

J Pharmacol Exp Ther. 2007;320(1):307-13

Endocrinology 1993;133:1300–1305

Follu Biol 1989;37(1-2):83-90.

Metabolism;9:293-5

Endocrinology 1977;101:453-463.

Reverse T3

- Reverse T3 suppresses T4 to T3 conversion

J. Clin Invest 1984;73:898-907

Endocrinology 1985;116(4):1627-1635

Follu Biol 1989;37(1-2):83-90.

Endocrinology 1977;101:453-463.

Endocrinology 1986;119(5):2186-2192

J Pharmacol Exp Ther. 2007;320(1):307-13

Reverse T3 (reduces metabolism)

- Reverse T3 decreases cellular energy production

Res Exp Med (Berl) 1997;197(4):211-7

Endocrinology 1993;133:1300–1305

Follu Biol 1989;37(1-2):83-90.

Metabolism;9:293-5

Reverse T3

Reverse T3 is a more potent inhibitor of T4 to T3 conversion than PTU.

(Medication used to decrease thyroid function in hyperthyroidism)

Chopra IJ. A study of extrathyroidial conversion of thyroxine (T4) to 3,3',5-triiodothyronine (T3) in vitro. Endocrinology 1977;101:453-463.

Thyroid Levels with chronic dieting

- Acute or chronic dieting can result in a significant decrease in intracellular and circulating T3 levels by up to 50%,[46,47,51,90] which significantly reduces basal metabolic rate (number of calories burned per day) by 15-40%.[48,230,232]
- When normal eating is resumed, thyroid levels and metabolism often **do not** return to normal.[48]

Holtorf, K. Thyroid Hormone Transport into Cellular Tissue J Restor Med 2014;3(1):53-68

Thyroid Levels with chronic dieting

- 25 days of calorie restriction (dieting) significantly reduced D1, resulting in reduced T4 to T3 conversion with a 50% reduction in T3.
- This dramatic reduction in T3 was associated with an increase in D2 (pituitary), so there was no increase in TSH but rather a decrease from an average of 1.20 ng/ml to 0.7 ng/ml.

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 Endocinol Metab 2009;296:E1157-E1163.

Thyroid Levels with chronic dieting

- Study by Leibel, et found that Individuals who significantly dieted in the past had, on average, 25% lower metabolism (equal to someone who weighed 60% less).
- Additionally, the reduction was shown to be present years later.
- This 25% percent reduction in metabolism equates to an approximate deficit of 500-600 kcal per day.

Leibel RL, Jirsch J. Diminished energy requirements in reduced-obese patients. Metabolism 1984;33(2):164-170.

Thyroid Levels with chronic dieting

The Effects of Repeated Cycles of Weight Loss and Regain in Rats

KE

Department of Psychiatry,

BROWNELL, K. D., M. R. C. GREENWO
weight loss and regain in rats. PHYSIOL B
weight cycling, i.e., repeated periods of weig
Dawley rats: (1) Chow Controls (a normal w
high-fat diet throughout); and (3) Obese Cy
refeeding). The cycled animals showed signifi
restriction and refeeding periods compared to
the rate in the second cycle. Several physio
experiment, cycled animals had a four-fold in
had not cycled. These data suggest that freq
metabolic and health consequences of "yo-y

Weight cycling Food efficiency Metabo

- Obese rats cycled through two cycles of calorie restriction
- In the 2nd cycle compared to the 1st, weight loss occurred at half the rate and regained at 3 times the rate in the 2nd cycle as the 1st
- At the end of the study, cycled animals had a 4-fold increase in food efficiency compared to obese animals that had not cycled

Thyroid Levels with insulin resistance and diabetes

- Numerous studies show that insulin resistance, diabetes and metabolic syndrome are associated with a significant reduction in T4 to T3 conversion, an intracellular deficiency of T3, and an increased conversion of T4 to reverse T3.[91,100,92,94,147,184-193,235]
- Additionally, the elevated insulin will increase D2 activity and suppress TSH levels, further decreasing thyroid levels [91-99,233]

Holtorf K, Diagnosis of hypothyroidism: Are we getting what we want from TSH testing? National Academy of Hypothyroidism (NAHypothyroidism.org)

Thyroid Levels with Insulin Resistance and Diabetes

- Diabetic individuals have a 42% reduction in T4 to T3 to T3 conversion

Pittman CS, Suda AK, Chambers JB, McDaniel HG, Ray GY. Abnormalities of thyroid hormone turnover in patients with diabetes mellitus before and after insulin therapy. JCEM 1979;48(5):854-60.

Thyroid Levels with insulin resistance and diabetes

- Investigated the T4 to T3 conversion in 50 diabetic patients compared to 50 non-diabetic controls.
- There was no difference in TSH and free T4 levels, but the diabetic individuals had 46% decrease in free T3 levels ($p = 0.0001$).
- The FT3/FT4 ratio was 50% less in diabetic patients versus controls.
- The TSH failed to elevate despite the fact that serum T3 was approximately half of normal.
- Saunders J, et al. also found that diabetics had approximately a 50% reduction in T3 levels and significantly increased reverse T3 levels and decreased T3/reverse T3 ratios.

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.

Saunders J et al. Thyroid hormones in insulin requiring diabetes before and after treatment. Diabetologia 1978;15:29-32.

Thyroid levels with insulin resistance and diabetes

- Investigated of the impact of supplemental T3 on cardiovascular risk in obese patients to partially reverse the reduced T4 to T3 conversion seen with obesity.
- 70 obese patients with "normal" standard thyroid function tests were treated with 20 mcg of straight T3 for six weeks.
- While the dose was not high enough to completely reverse the reduced T4 to T3 conversion seen with obesity, there was a significant reduction in a number of cardiovascular risk factors, including cholesterol and markers for insulin resistance.
- There were no side-effects in any of the patients.
- The authors conclude, *"T3 may be considered to ameliorate some of the risk factors associated with abdominal obesity, particularly in some subgroups of obese women with a relative resistance to thyroid hormones possibly dependent on decreased peripheral deiodination of thyroxine (T4)."*

Krotkiewski M. Thyroid hormones and treatment of obesity. Int J of Obesity 2000;24(2):S116-S119

Thyroid and Pain

- Chronic pain will significantly suppress D1 and upregulate D2, resulting in a reduction in tissue T3 without a change in TSH.[116-119]

Holtorf K, Diagnosis of hypothyroidism: Are we getting what we want from TSH testing? National Academy of Hypothyroidism (NAHypothyroidism.org)

Thyroid and Pain

- Narcotics also suppress D1 but not D2, so such treatment is ineffective at reversing the suppressed tissue T3 levels.[116-118,229]
- Tolerance to the inhibitory effect of narcotics on TSH secretion and T4 to T3 conversion does not occur.[116,119]
- Pain specialists are starting to understand this and are recommending T3 supplementation to patients with significant pain or on narcotic pain medications.[229]

Holtorf K, Diagnosis of hypothyroidism: Are we getting what we want from TSH testing? National Academy of Hypothyroidism (NAHypothyroidism.org)

Thyroid Hormone Transport

- The common belief that T4 and T3 diffuse into the cell has been shown to be totally incorrect.[1-43]
- It has been shown that active thyroid hormone transport is the rate-limiting step in the determination of thyroid activity.[5,20,41,44,45]
- This transport has nothing to do with diffusion, but rather it is energy requiring active transport.[1-43,45,46,47, 48-64,65,66,67]
- The incorrect "diffusion hypothesis," however, continues to be taught in medical school and is believed to be true by most physicians and endocrinologists

Holtorf, K. Thyroid Hormone Transport into Cellular Tissue J Restor Med 2014;3(1):53-68

Thyroid Hormone Transport

- Because TT is energy dependent, any condition associated with a reduced production of the cellular energy (mitochondrial dysfunction) will also be associated with reduced transport of thyroid into the cell, resulting in cellular hypothyroidism despite having standard blood tests in the "normal" range

Holtorf, K. Thyroid Hormone Transport into Cellular Tissue J Restor Med 2014;3(1):53-68

Thyroid Hormone Transport

- Conditions associated with reduced mitochondrial function and impaired thyroid transport include: insulin resistance, diabetes and obesity;[68,69,70,71,106] chronic and acute dieting;[4,51,66,72,112,113,114,115,116,117,118] diabetes;[69,73,74,75,76] depression; [73,77,78,79] anxiety;[73,80] bipolar depression; [73,77,81,82] neurodegenerative diseases;[73,83,84,85,86,87)] aging;[73,74,88-100] chronic fatigue syndrome; [73,101,102] fibromyalgia; [73,103,104] migraines; [73] chronic infections; [73] physiologic stress and anxiety; [73,79] cardiovascular disease; [73,99,104,105,108] inflammation and chronic illness; [73,109,110,111] and those with high cholesterol and triglyceride levels. [58,60,72,106,107]

- Thus, standard blood tests can be very unreliable if any of these commonly occurring conditions are present.[1-107]

Holtorf, K. Thyroid Hormone Transport into Cellular Tissue J Restor Med 2014;3(1):53-68

Reverse T3
(blocks cellular uptake of T4 and T3)

Placenta (1999), 20, 65–70

Uptake of Reverse T_3 in the Human Choriocarcinoma Cell Line, JAr

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Australia

Paper accepted 13 July 1998

The uptake and e ux of reverse triiodothyronine (rT_3) in JAr cells were investigated. Uptake of ^{125}I-rT_3 was time dependent and reversible with a saturable component of around 70 per cent of total uptake after 30 min of incubation. E ux was not saturable. Kinetic analysis of the initial specific uptake rates revealed an uptake process with a Michaelis constant of 3.04 ± 0.53 µ (mean ± , $n=15$) and a corresponding maximum velocity of 9.65 ± 2.49 pmol/min/mg protein ($n=15$). Uptake of rT_3 was stereospecific, but not specific for rT_3, as unlabelled stereoisomers of thyroid hormone analogues were more e ective as inhibitors of ^{125}I-rT_3 uptake than rT_3. Unlabelled T_3 and thyroxine (T_4) (10 µ) reduced cellular uptake of ^{125}I-rT_3 by around 82 and 74 per cent, respectively. The calculated inhibition constants K_i were 1.23 ± 0.29 µ ($n=4$) and 0.66 ± 0.19 µ ($n=4$) for T_3 and T_4, respectively. Similarly, rT_3 reduced cellular uptake of ^{125}I-T_3 and ^{125}I-T_4 by 34 and 23 per cent, respectively. The calculated inhibition constants K_i were 1.75 ± 0.55 µ ($n=8$) and 1.08 ± 0.36 µ ($n=8$) for the inhibition of ^{125}I-T_3 and ^{125}I-T_4 uptake, respectively. Reverse T_3 inhibited e ux of ^{125}I-T_3 from the cells by around 20 per cent, but did not inhibit e ux of ^{125}I-T_4. These results suggest that uptake of rT_3 in JAr cells may occur via a single, saturable membrane carrier, which also interacts with T_3 and T_4, while e ux of rT_3 may occur by passive di usion.

Reverse T3 blocked cellular uptake of T3 by 34% and T4 by 23%.

Thyroid Hormone Transport

- When cell cultures are incubated with the serum from physiologically stressed or dieting individuals; there is shown to be a dramatic reduction of the uptake of T4 by the cells that correlates with the degree of stress.[41,42,50]

Holtorf, K. Thyroid Hormone Transport into Cellular Tissue. J Restor Med 2014;3(1):53-68

Thyroid Hormone Transport (stress)

- Serum from non-stressed individuals had no effect on T4 cellular uptake, while those with significant physiologic stress had up to a 44% reduction in T4 uptake into the cell.
- It was shown that the free T3/reverse T3 ratio was the most accurate marker for reduced cellular uptake of T4.

Vos RA et al. Impaired thyroxine and 3,5,3'-triiodothyronine handling by rat hepatocytes in the presence of serum of patients with nonthyroidal illness. J Clin Endocrinol Metab 1995;80:2364-2370

Thyroid Hormone Transport (dieting)

- With repeated cycles of dieting, weight loss occurred at half the rate and weight gain occurred at three times the rate compared to controls with the same calorie intake.[118]
- Chronic and yo-yo dieting, frequently done by a large percentage of the population, is shown to be associated with reduced cellular T4 uptake of 25%-50%.[3,49,112,114,115,116]

Holtorf, K. Thyroid Hormone Transport into Cellular Tissue. J Restor Med 2014;3(1):53-68

Thyroid Hormone Transport (depression)

- The dysfunction present with depression and bipolar depression includes down regulation of D1 (reduced T4 to T3 conversion) and reduced uptake of T4 into the cell.[24-26,30,31,35,39-45]
- Thought to have "high normal" levels of thyroid—usually low normal TSH and high normal T4.
- Lack of benefit from T4 used as proof by doctors to "prove" the patient is not hypothyroid.
- T3 stimulates production of serotonin

References: Holtorf, K. Thyroid Hormone Transport into Cellular Tissue J Restor Med 2014;3(1):53-68

Thyroid Hormone Transport (depression)

- Additionally, studies show that depressed patients have reduced T4 transport across the blood brain barrier due to a defective transport protein, transthyretin.[23,39,40]
- Have significantly reduced thyroid levels in the brains of depressed patients despite "normal" serum levels and standard thyroid tests.[23,39,40] as well as a reduced TSH response to TRH.[28-31,43-50]

Holtorf, K. Thyroid Hormone Transport into Cellular Tissue J Restor Med 2014;3(1):53-68

T3 and depression

- T4 and T4/T3 combinations may have some benefit in depression; but due to the suppressed T4 to T3 conversion from suppressed D1 and reduced uptake of T4 into the cell and brain, T3 is significantly more beneficial than T4 or T4/T3 combination supplementation.[25,41,202,220,225-227]

References: Holtorf, K. Thyroid Hormone Transport into Cellular Tissue J Restor Med 2014;3(1):53-68

T3 and depression

- Double blind placebo control trial of 50 patients with normal thyroid function as defined by a normal TSH (1.5 +/- 0.8).
- The patients were randomized to receive 25 mcg of T3 or placebo in addition to antidepressant therapy.[221]
- The study found almost a 2-fold increase in response rate with T3 and a 4.5 times greater likelihood of experiencing a positive response at any point over a six-week period with the addition of T3.
- Side effects were higher in placebo group on 10/11 criteria including a significant increase in nervousness with the placebo group

Posternak M et al. A pilot effectiveness study: placebo-controlled trial of adjunctive L-triiodothyronine (T3) used to accelerate and potentiate the antidepressant response. Int J Neuropsychopharmacology 2008;11:15–25.

T3 and bipolar depression

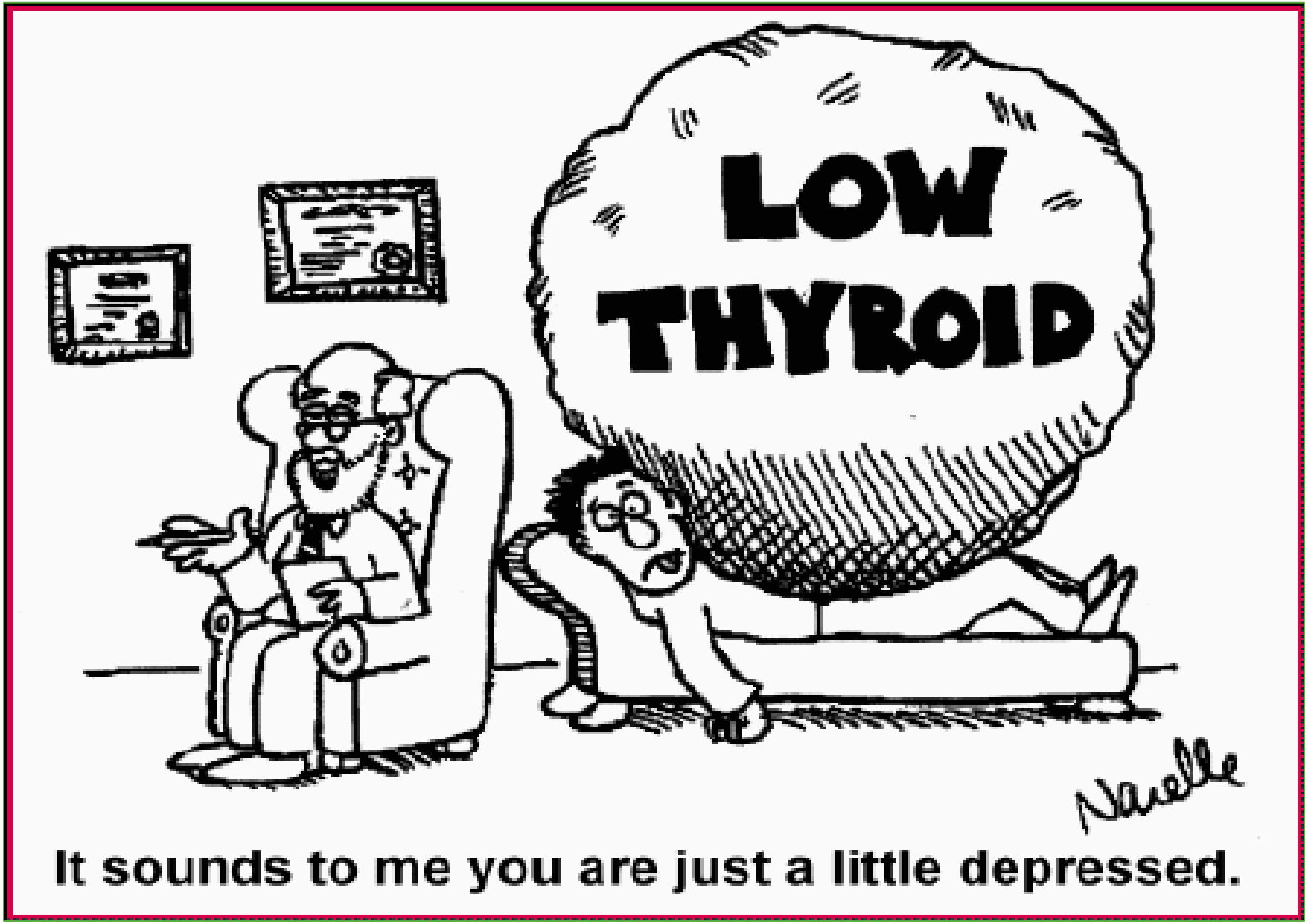
- Treated 159 bipolar patients with T3 who had failed to adequately respond to an average of 14 medications (average dose 90.4 mcg (range 13 mcg-188 mcg)).
- The medication was found to be well tolerated and 84% experienced significant improvement and 33% had a full remission.
- One patient who was switched to T4 for cost reasons experienced a return of symptoms, which resolved with the reintroduction of T3.
- The authors concluded, "*Augmentation with supraphysiologic doses of T3 should be considered in cases of treatment resistant bipolar depression…*"
- The authors thanked several doctors who encouraged them to go beyond the traditional 50 mcg of T3 because it has helped so many of their patients.

Kelly T et al. The use of triiodothyronine as an augmentation agent in treatment resistant bipolar II and bipolar disorder NOS. Journal of Affective Disord 2009;116:222-226.

T3 and depression

- With over 4000 patients, The Star*D Report is the largest trial comparing antidepressant effectiveness for depression.
- It found that 66% of patients fail to respond to antidepressants or have side-effects severe enough to discontinue use.
- Of those who do respond, over half will relapse within one year.
- The trial found that T3 was effective even when other medications -- such as citalopram (Celexa), bupropion (Wellbutrin), sertraline (Zolft), venlafaxine (Effexor), or cognitive therapy – were not.
- It was shown to be 50% more effective, even with the less than optimal dose of 50 mcg, under direct comparison with significantly less side effects than commonly used therapeutic approaches with standard antidepressants.

Nierenberg AA et al. A comparison of lithium and T3 augmentation following two failed medication treatments for depression: A STAR*D Report. Am J Psychiatry 2006;163:1519-1530.



Brian Narelle

Case Study #1

- 42 y/o women comes in complaining of inability to lose weight, ongoing depression on antidepressants, fatigue and muscle pain. She has been diagnosis with fibromyalgia, bipolar depression and type II diabetes.
- She is on metformin and Effexor, Vicodin for pain and Lipitor. She has tried numerous antidepressants and Lyrica without benefit.
- She brings in labs showing a TSH of 1.2, free T4 of 1.7 (0.8-1.8) and a free T3 of 2.7 (2.3-4.2).

Case Study #1

What is the chance this patient has low thyroid levels contributing to her symptoms?

Case Study #1

What is the chance this patient has low thyroid levels contributing to her symptor

- **Being overweight**
  - 36% chance of being low thyroid (Donders, et al);
  - All obese patients had thyroid dysfunction (Ford et al).
  - Giving 50 mcg of T3 to obese patients partially compensated for their inherent thyroid deficiency with resultant improvement in CV risk factors such as elevated cholesterol and insulin resistance (Krotkiewski, et al)
- **Chronic dieting**
  - 50% reduction in T4 to T3 conversion (no change in TSH) with chronic dieting (Araujo, et al)
  - 25% lower metabolism with chronic dieting (Leibel, et al)
- **Diabetes**
  - 42% reduction in T4 to T3 conversion (Pittman et al)

(continued next slide)

Case Study #1 cont.

- **Depression (bipolar)**
  - Giving T3 is safer and more effective than antidepressants (Kelly, et al, Posternak, et al and Star*D report).
- Statins artificially lower TSH, making the TSH unreliable (Seth, et al)
- Low-normal thyroid is associated with higher CV risk than having high cholesterol, HTN, diabetes or smoking (Hak et al).

Case Study #1

What tests can be done to evaluate the presence of thyroid resistance?

Case study #1[2]

What can be done to further evaluate her thyroid function?

- Signs/symptoms: She was found to have low body temp (97.4), inability to lose weight, dry skin, constipation, course skin (heel & elbows), cold skin and extremities- Zulewski, et al showed that combination of more than five very common symptoms has a positive predictive value of being hypothyroidism > 96.9%.
- Visually had a slow relaxation phase of ankle reflex and confirmed with a Thyroflex test of 190ms (normal < 110ms). Shown by Maier, et al in BMJ to be a better determinant of hypothyroidism than an elevated TSH.
- Found to have a low resting metabolic rate (RMR)-22% lower than expected for a person of her weight and gender, which is a gold standard for hypothyroidism (hypometabolic).

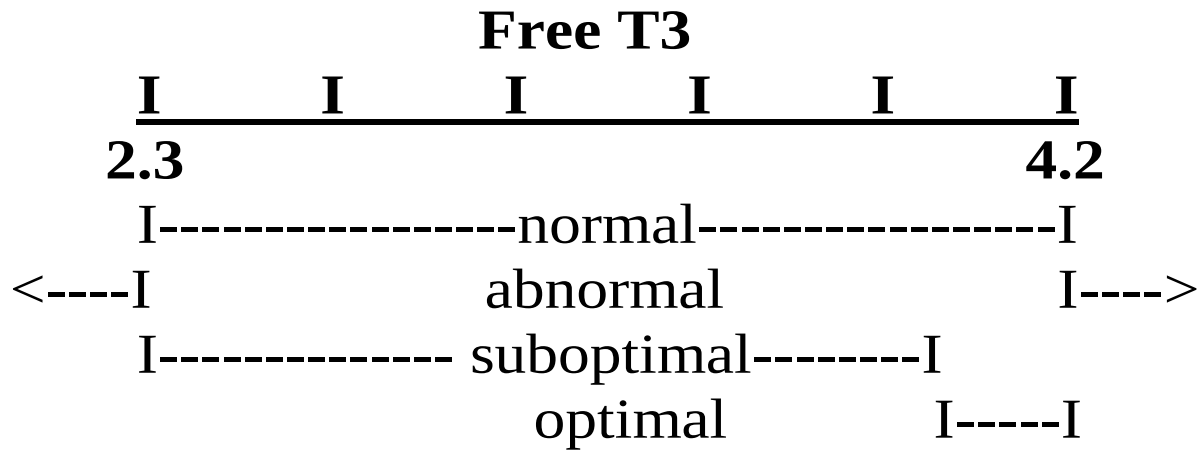
Meier C, et al. Serum thyroid stimulating hormone in assessment of severity of tissue hypothyroidism in patients with overt primary thyroid failure: cross sectional survey. Brit Med J 2003;326:311-312

Case Study #1

What if lab tests reveal:

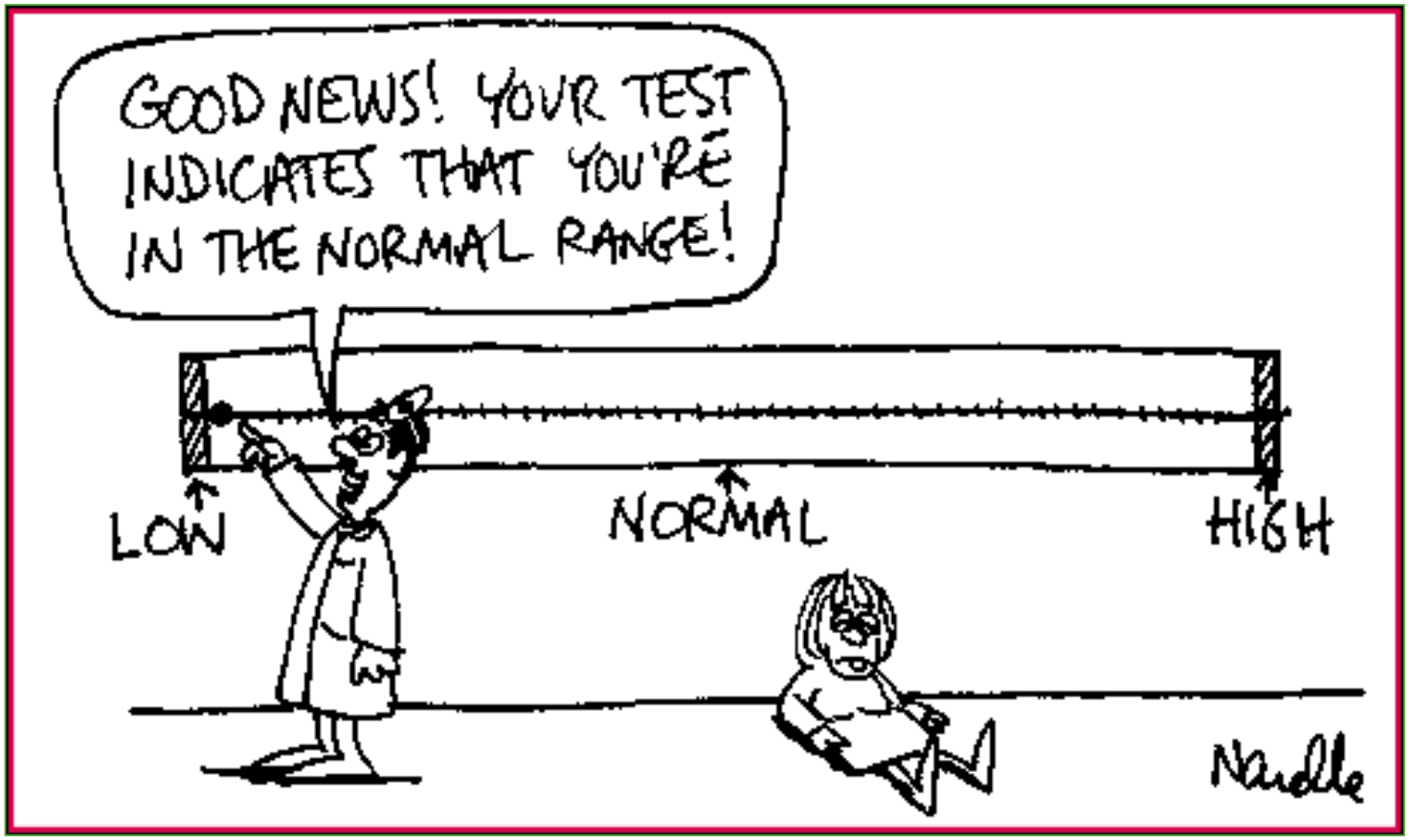
- SHBG 32 mg/dl (>70): **measure of tissue (liver) thyroid levels**
- HgA1c 6.1: **Diabetics have 30-50% decreased T4-T3 conversion and lower TSH**
- Leptin 22 (< 12): **Leptin resistance (TSH not reliable)**
- Insulin 16 **(IR associated with suppressed TSH and decreased T4 to T3 conversion)**
- CRP 3.2 (<1.0): **Reduced T4-T3 conversion and suppressed TSH**
- D-dimer 1.8 (<0.5); PTF 1&2, SFM and TAT complex elevated: Positive Immune Activation of Coagulation—**thyroid resistance**
- High Trig or low HDL: metabolic syndrome—**decreased T4-T3 conversion**
- C4a 22,000 (<2250): **Significant inflammation—thyroid resistance (consider chronic infection/Lyme disease workup)**

Diagnosis (physical exam)



- The overwhelming percentage of people who suffer from low thryoid will fall in the normal but suboptimal range.
- Bringing T3 to more optimal levels can have profound results.

Diagnosis (laboratory)



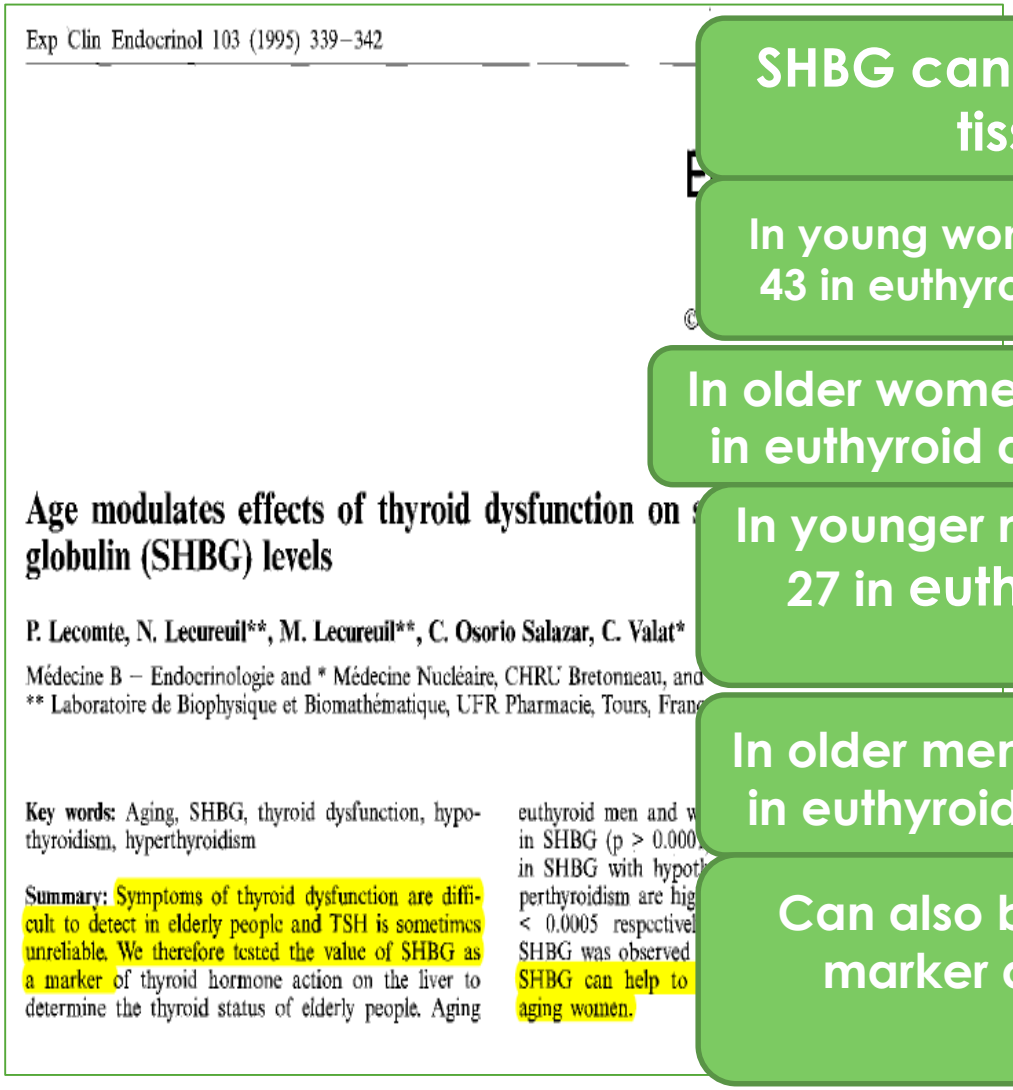
Brian Narelle

Diagnosis (laboratory)

Best method of diagnosis

- Free T3 should be above 3.5
- Reverse T3 less than 150
- TSH greater than 2.0 is significant
- Usually low normal free T3 and above average reverse T3
- Look at T3 to reverse T3 (T3/rT3)ratio (should be >2)
- Signs and symptoms (body temp, pulse, cold extremities, etc)
- SHBG < 70 for women; < 30 for men
- Relaxation phase ankle reflexes
- Basal metabolic rate
- Leptin > 12
- Any positives on TMP
- High C4a, ECP

Diagnosis (SHBG)



Exp Clin Endocrinol 103 (1995) 339–342

Age modulates effects of thyroid dysfunction on s globulin (SHBG) levels

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Key words: Aging, SHBG, thyroid dysfunction, hypothyroidism, hyperthyroidism

Summary: Symptoms of thyroid dysfunction are difficult to detect in elderly people and TSH is sometimes unreliable. We therefore tested the value of SHBG as a marker of thyroid hormone action on the liver to determine the thyroid status of elderly people. Aging

euthyroid men and w
in SHBG ($p > 0.000$
in SHBG with hypoth
perthyroidism are hig
< 0.0005 respectivel
SHBG was observed
SHBG can help to
aging women.

SHBG can be used as a measure of tissue thyroid levels.

In young women, average SHBG was 24 in hypo, 43 in euthyroid and 153 in hyperthyroid patients

In older women SHBG averaged 37 in hypo, 69 in euthyroid and 115 in hyperthyroid patients

In younger men, SHBG averaged 15 in hypo, 27 in euthyroid and 107 in hyperthyroid patients

In older men, SHBG averaged 42 in hypo, 54 in euthyroid and 83 in hyperthyroid patients

Can also be helpful for follow-up as a marker and support for adequate replacement

Diagnosis (SHBG)

Sex Hormone-Binding Globulin in the Diagnosis of Peripheral Tissue Resistance to Thyroid Hormone: The Value of Changes after Short Term Triiodothyronine Administration*

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Departments of Medicine and Pediatrics, University of Chicago, Chicago, Illinois 60637

ABSTRACT. Thyroid hormone is one of several factors that modulate the level of sex hormone-binding globulin (SHBG) in serum. SHBG levels are usually elevated in thyrotoxicosis and have been reported to be normal in a few patients with generalized resistance to thyroid hormone (GRTH). This study was designed to determine whether basal serum SHBG levels or the SHBG response to short term T_3 administration could be used as an index of thyroid hormone action and thus serve as a test for the evaluation of patients suspected of having peripheral tissue resistance to thyroid hormone. Serum SHBG, total T_4, free T_4 index (FT_4I), total T_3, and TSH levels were measured in 21 normal subjects, 28 hypothyroid patients, 20 thyrotoxic patients, and 10 patients with GRTH.

Excluding patients with GRTH, serum basal SHBG values were correlated with FT_4I values ($r = 0.66$; $P < 0.0001$). Mean SHBG levels in the patients with GRTH [37.6 ± 16.2 (±SD) nmol/L] were not significantly different from those in the normal subjects (35.1 ± 19.3 nmol/L) or hypothyroid patients (26.3 ± 17.1 nmol/L), but were significantly lower than those in the thyrotoxic group (64.7 ± 19.2 nmol/L; $P < 0.001$). All 10 patients with GRTH had basal SHBG values in the normal range, but 7 of 20 (35%) thyrotoxic patients also had normal basal SHBG values.

T_3 was given orally for three sequential 3-day periods at doses of 50, 100, and 200 μg daily to 7 normal subjects, 11 hypothyroid and 3 thyrotoxic patients, and all 10 patients with GRTH. The serum SHBG concentration was measured on the last day at each dosage level. During T_3 adm
creased in all individuals with norm
increase above the basal value (Δ
similar in normal, hypothyroid, and
resistant subjects). After administ
mean ΔSHBG level was decreased
in the resistant patients and increa
0.005) in the nonresistant subjects. A
μg T_3 daily, the mean ΔSHBG was −4.5 ± 6.8 nmol/L in the resistant patients and 8.6 ± 5.1 nmol/L ($P < 0.0001$) in the nonresistant subjects. Serum SHBG decreased by more than 2 nmol/L in 6 of 10 (60%) resistant patients, but in no nonresistant subject. After administration of 200 μg T_3 daily, the mean ΔSHBG increase was 0.7 ± 7.3 nmol/L in the resistant patients and 16.6 ± 7.3 nmol/L ($P < 0.0001$) in the nonresistant subjects.

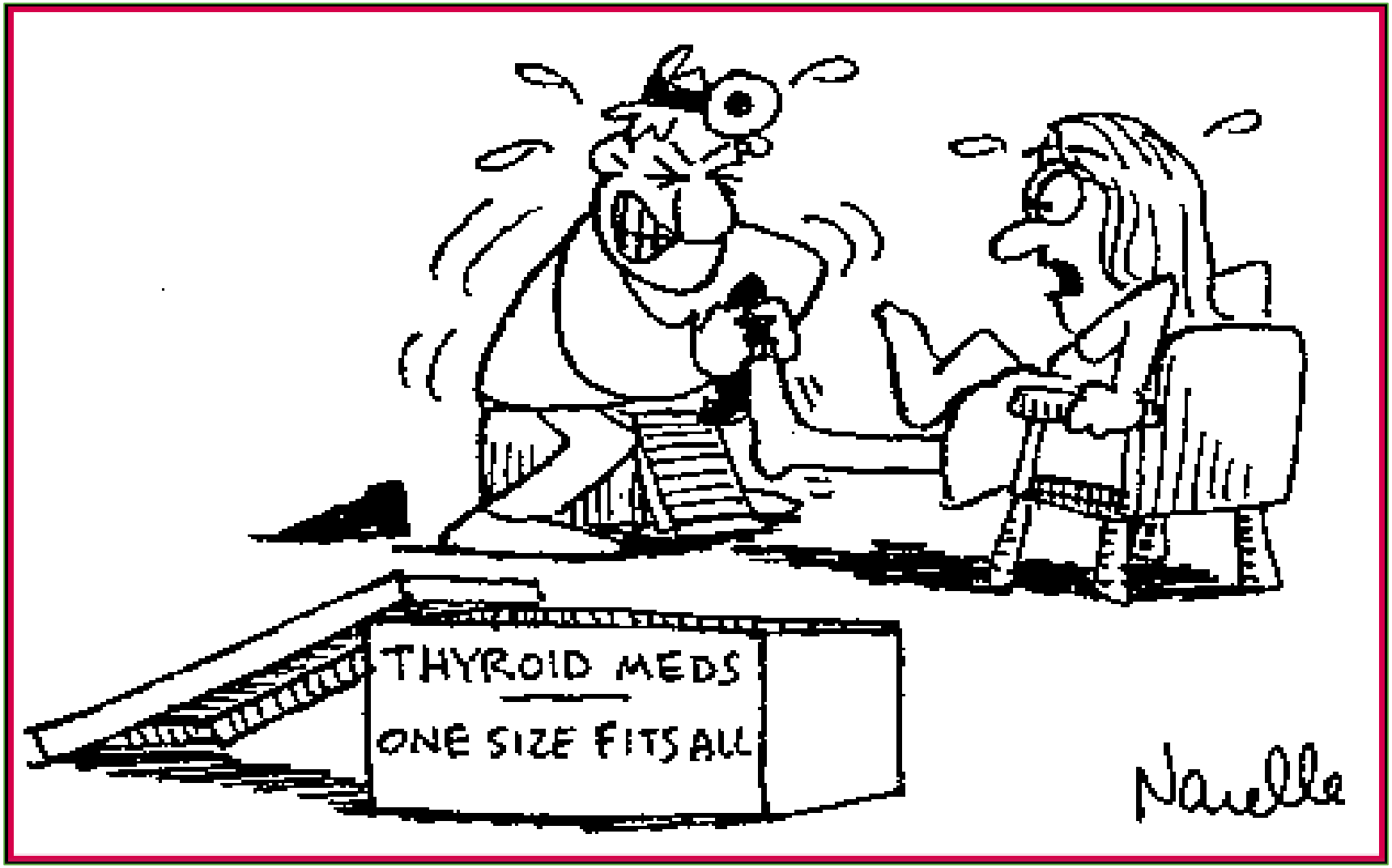
Neither the combination of a normal basal serum SHBG value and elevated serum thyroid hormone values nor the relationship between serum SHBG and FT_4I values was sufficient to separate all GRTH patients from those with thyrotoxicosis. The combination of elevated serum thyroid hormone values and failure of serum SHBG to increase above the basal value after the administration of T_3 for 6 days was found in 9 of 10 patients with GRTH but in none of the thyrotoxic subjects. The response of SHBG to T_3 administration is useful in the demonstration of peripheral tissue resistance to thyroid hormone. (*J Clin Endocrinol Metab* **66:** 740, 1988)

SHBG will increase with the administration of T3 in normal individuals but not in those with thyroid resistance

Treatment with Positive Outcome (Preparations)

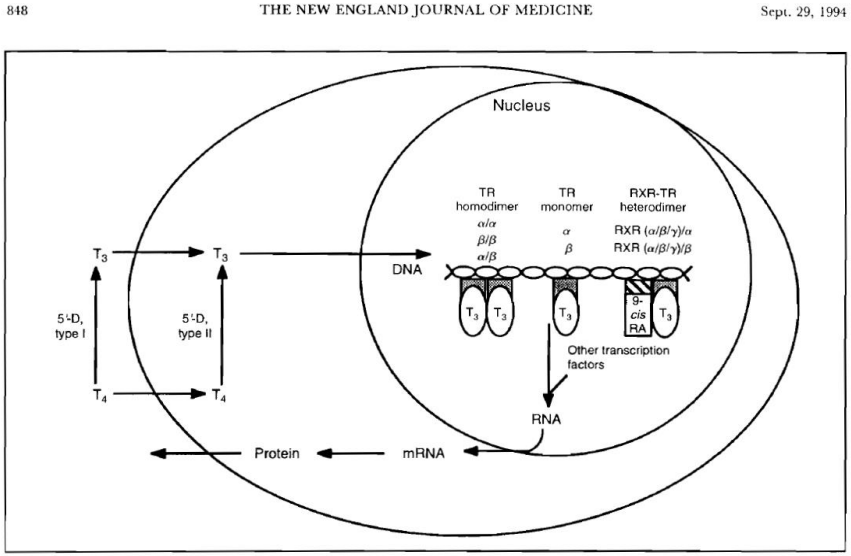
- T4 Synthroid, Levoxyl
- T4/T3 Armour, compounded, Thyrolar
- T3 Cytomel
- T3 timed released (compounded T3)

Treatment with Positive Outcome (Preparations)



T3 SR vs. Cytomel

- Thyroid hormone action is genomic (in the nucleus)—via the binding of T3 with nuclear receptors that bind to regulatory genes that modify mRNA translation and protein synthesis.
- Steady serum levels generally not as important with genomic actions, as they require protein synthesis take days to weeks to take effect.



T3 SR vs. Cytomel

- Also, nongenomic actions that interact with the plasma membrane and effect ion pumps or channels
- Nongenonic actions are generally rapid in onset (seconds to minutes)
- Independent of nuclear effects

1. Incerpi et al. Short-term effects of thyroid hormone on the Na/H antiport in L-6 myoblasts: high molecular specificity for 3,3.,5-triiodo-L-Endocrinology 1999;140:683-689
2. Z-Q Sun et al. Effects of thyroid hormone on action potential and repolarizing currents in rat ventricular myocytes. Am J Physiol 2000;2778:E302-E307
3. Y Sakaguchi et al. Acute effects of thyroid hormone on inward rectifier potassium channel currents in guinea pig ventricular myocytes. Endocrinology 1999;137:4744-4751

T3 SR vs. Cytomel

- Major nongenomic action includes activation of cardiac Na+/Ca+/K+ channels.
- Increases cardiac contractility and heart rate
- Thus, stable serum T3 are important to reduce potential cardiac side-effects.
- Can potentially use Cytomel tid/qid but compliance issues.

T3 SR vs. Cytomel

- Methocel (substance that makes T3 SR time-released will bind-up T3 and decrease absorption)
- Cytomel and T3 dosage are not interchangeable
- T3 SR about 1/3rd to 4/5th as potent as Cytomel
- Trade-off of appearance of high dose for steady levels of T3

Potency of T4 vs. T3

Listed Equivalencies

Drug	Thyroid Tablets, USP (Armour® Thyroid)	Liothronine Tablets, USP (Cytomel®b)	Levothyroxine Tablets, USP(Unithroid®c Levoxyl®d, Levothroid®e, Synthroid®f)
Approx. Dose Equivalent	1/4 grain (16.25 mg)	6.25 mcg	25 mcg (.025 mg
Approx. Dose Equivalent	1/2 grain (32.5 mg)	12.5 mcg	50 mcg (.05 mg)
Approx. Dose Equivalent	1 grain (65 mg)	25 mcg	100 mcg (0.1 mg
Approx. Dose Equivalent	1 1/2 grains (90 mg)	37.5 mcg	150 mcg (0.15 m
Approx. Dose Equivalent	2 grains (120 mg)	50 mcg	200 mcg (0.2 mg
Approx. Dose Equivalent	3 grains (180 mg)	75 mcg	300 mcg (0.3 mg

Listed that 1 gr (38T4/9T3) is equivalent to100 of T4

If that is true, T3 would have to be 6.9 times the potency of T4 (100 - 38 = 62: 62/9 = 6.9)

If T3 is 4 x's as potent than 1 grain would equal 75 T4.

If 2 times than 1 gr equivalent to 56 of T4

Treatment with T4

T4 preparations are not optimal or adequate for patients who have CFS/FM, depression, chronic illness, diabetes, Lyme dz, weight gain, etc. because they have a high incidence of reduced T4 to T3 conversion, reduced uptake of T4 and thyroid resistance.

Treatment with T4 (tissue levels of T3)

- Studied whether or not, tissue specific regulatory mechanisms provide normal T3 concentrations simultaneously in all tissues in hypothyroid animals receiving T4 only thyroid replacement
- Plasma TSH, T4 and T3 levels and 10 different tissue levels of T4 and T3 were measured after the infusion of 12-13 days of thyroxine. Also measured tissue deiodinase activity

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 96:2828-2838

Treatment with T4

- Demonstrated that all tissues, except the brain, required supraphysiologic levels of plasma T4 to provide normal tissue levels of T3.
- The exception was the brain (which includes the pituitary). This demonstrates that the pituitary will be able to maintain normal levels of T3 despite the rest of the body being hypothyroid.
- Consequently, the pituitary levels of T3 and subsequent level of TSH is a poor measurement of tissue hypothyroidism as it may not be elevated when the rest of the body is severely hypothyroid

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 96:2828-2838

Treatment with T4

- Demonstrated that it is impossible for T4 only preparations such as Synthroid or Levoxyl to achieve normal levels of T3 in all tissues, except the brain and pituitary, unless supraphysiologic levels of T4 and T3 are obtained and the TSH is suppressed
- T4/T3 combinations are required to normalize tissue levels of T4 and T3.

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 96:2828-2838

Treatment with T4

- Normal T4 or T3 levels did not ensure tissue euthryoidism
- Supraphysiologic plasma T4 and T3 levels were required to obtain normal levels in some tissues
- At some amounts of T4 infused, the level of thyroid hormones in the pituitary was over twice that of other tissues, again demonstrating that pituitary levels and thus TSH secretion is not an accurate measure of tissue hypothyroidism.

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 96:2828-2838

Treatment with T4

- Doses of T4 that normalized plasma T4 and T3 levels was insufficient to normalize the concentration of T3 in peripheral tissues
- Exception: Brain and pituitary
- Why do we use the TSH?

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 96:2828-2838

Treatment with T4

"It is evident that neither plasma T4 nor plasma T3 levels alone permit prediction of the degree of change in T4 and T3 concentrations in tissues: not lonely are the tissue to plasma T4 and t3 ratios different for different tissue, but they may also change for a single tissue as a function of the plasma iodothyronine level."

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 96:2828-2838

Treatment with T4

"It is clear for the present results that a normal thyroid status is not achieved simultaneously for all tissues when T4 alone is infused."

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 96:2828-2838

Treatment with T4

"The current replacement therapy of hypothyroidism should no longer be considered adequate, and might possibly lead to the development of new strategies of therapy combining administration of both T4 and T3."

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 96:2828-2838

Optimal Thyroid Replacement (dosing)

- Consider Wilson's Thyroid Protocol (especially if low body temp)
- T3-Start low and titrate up
  - T3 10 mcg x 10 days, then
  - 15 mcg x 10 days, then
  - 25 mcg then
  - increase by 12.5 mcg every 2 to 4 weeks
  - Start at 5 mcg if > 60 Years old or any risk of CAD, after a stress test and/or vascular ultrasound
- T4/T3-start low and titrate up
  - T4/T3 0.5 grain x 10 days, then
  - 1 grain x 10 days, then
  - 1.5 grain x 30 days
  - Start O.25 grains if > 60 or any risk of CAD

Optimal Thyroid Replacement (monitoring)

- Can trigger caffeine-like anxiety, palpitations or insomnia
- Can be relieved with reduction in dose, beta blockers, Cardio Care, Mg+.
- Like exercise, if someone is on the brink of a heart attack, giving thyroid could trigger it. True risk very low because thyroid causes coronary artery dilatation and long-term reduced risk of heart disease
- If chest pain, likely panic attack, but on very rare occasion consider referral to ER, etc.

Optimal Thyroid Replacement (dosing)

- Continue to slowly increase T3 by 12.5 to 25 mcg
  - (50 mcg to 62.5 x 10 days, then 75 mcg, Reassess next visit)
- Base dose on symptoms, thyroid hormone levels, TSH, SHBG, side effects, pulse, body temperature, speed of RPBRR and RMR.
- T3 norms are for giving T4, which goes into the cell and a small amount of T3 diffuses into the blood.
- When giving T3, can have abnormally high T3 levels, low T4 and a suppressed TSH

Optimal Thyroid Replacement (monitoring TSH)

The false positive rate that a suppressed TSH indicates hyperthyroidism in someone on thyroid replacement is 80%

The positive predictive value of a suppressed TSH is demonstrating hyperthyroidism is equal to:

$$\text{Positive predictive value (PPV)} = \frac{\text{sensitivity x prevalence}}{((100\text{-specificity}) \times (100\text{-prevalence})) + (\text{sensitivity x prevalence})}$$

$$\frac{59 \times 20}{(100-51) \times (100-20) + (59 \times 20)}$$

$$\frac{1180}{49 \times 80 + 1180} = 23\ \%$$

Meier C et al. Serum TSH in assessment of severity of tissue hypothyroidism in patients with overt primary thyroid failure: cross sectional survey. The British Medical Journal 2003;326:311-2.

Optimal thyroid replacement
(monitoring TSH)

- A person on thyroid replacement with a suppressed TSH has a 23% chance of being hyperthyroid.
- In addition, this is in individuals with no known pituitary dysfunction.
- Patients with CFS/FM, inflammatory disorder, Lyme disease, autoimmune disease, diabetes or insulin resistance, depression, and those who are obese, dieting or stressed have pituitary dysfunction which lowers the PPV and increases the false positive rate of the suppressed TSH indicating hyperthyroidism.

Meier C et al. Serum TSH in assessment of severity of tissue hypothyroidism in patients with overt primary thyroid failure: cross sectional survey. The British Medical Journal 2003;326:311-2.

Conclusion

- Thyroid resistance is the most common form of hypothyroidism
- Causes include, CFS/FM, diabetes, inflammation, depression, obesity, dieting, stress, chronic infection, chronic pain, leptin resistance, toxin exposure.
- It is inappropriate to rely on or require an elevated TSH before treatment with thyroid replacement. Standard reference ranges do not apply
- T4 replacement is not a good choice in such patients (all but the healthiest) because of defective T4 to T3 conversion, excess production of rT3, poor T4 transport into the cell, resistance due to fibrin deposition and blockage of receptor and post binding translation (activity).

Thank you

Questions?

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Medical Director/CEO, National Academy of Hypothyroidism
KHolt.@HoltorfMed.com