DPC SUMMIT

WHEN ”NORMAL” TSH ISN’T NORMAL

Why guidelines-based treatment is imperfect for so many and what to do instead

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- Navigate to https://aafp1.cnf.io/ and tap the session titled "When “Normal TSH” Isn’t Normal"
- OR just point your phone’s camera at the QR code to join directly

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Learning Objectives

1. Recognize the subset of patients who have a constellation of symptoms indicating hypothyroidism and "Normal labs" who would benefit from specific, balanced thyroid replacement.
2. Learn 3 lab presentations that indicate inadequate thyroid signaling even when TSH is normal, and why they happen.
3. Learn a simple way to replace thyroid hormone using a combination of T3 and T4 which normalizes symptoms without suppression of TSH.

(Ref: 2, 4, 5, 6)

Learning Objectives

- Why TSH and guidelines based thyroid management doesn't always normalize patients who are clinically hypothyroid.
- Who to test beyond just TSH with reflex to T4
- A simple test panel to get better answers for your patients and guide treatment
- **Safe use of T3 and T3 combinations to get consistently better outcomes**

Why Me? (I'm an ENT)

Symptoms of Hypothyroidism

Thyroid hormone controls the way our body makes and uses energy. Our cells depend on thyroid to stimulate transcription and protein synthesis, drive ATP production, and the function of each tissue type. The result of deficiency is vague and nonspecific symptoms

- Fatigue - sluggishness
- Mental Impairment
  - Depression, anxiety
  - Poor memory
  - Slow executive function
  - Decision making problems
- Poor quality sleep
- Not rested despite extended sleep schedule
- Feeling cold – low body temperature
- Icy, even aching, hands and feet
- Muscle and Joint Pain
- Poor immune function – increased allergy and infections
- Low blood pressure
- Heart - palpitations or bradycardia
- Menstrual problems – painful and irregular cycles, Low LH and FSH
- Infertility, miscarriages
- Constipation and reflux
- Dry, itchy skin
- Hair loss
- Brittle nails
- Facial and peripheral edema
- Metabolic changes - weight gain,
- Elevated Cholesterol (8, 9)

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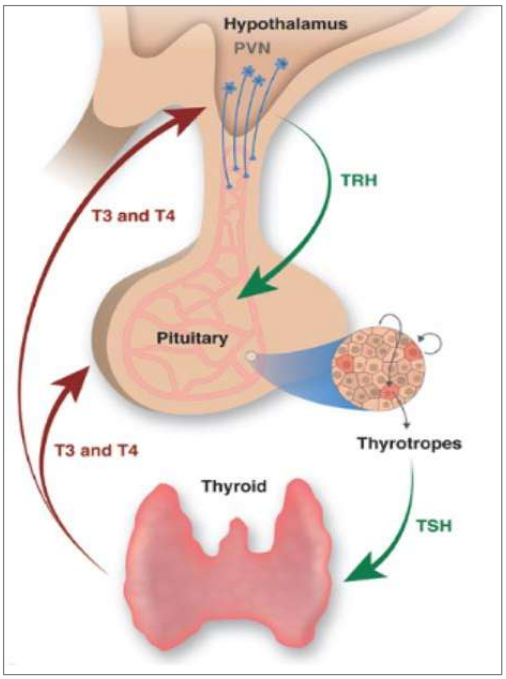
HPT Axis Regulation of Thyroid Levels

- Hypothalamus senses lowT4, sends TRH to the pituitary
- Pituitary releases TSH to the bloodstream
- Thyroid gland releases T3 and T4
- Thyroid hormone travels bound to proteins to the tissues where it is needed

(10, 11, 12, 13)



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Biochemically euthyroid patients are not well compared to euthyroid controls

NHANES population analysis

- As a class, chemically euthyroid patients treated with T4 have poorer outcome measures as compared to TSH matched euthyroid controls (14)
  - More likely to be taking beta-blockers, statins, and antidepressants (13)
  - Higher BMI - despite lower caloric intake
  - Unresolved cognitive impairment
  - Abnormal lipids (15)
  - QOL impairments (16, 17)
  - More frequent Cardiac Events (18)
  - Increased All Cause Mortality (19, 20, 21)

WHY are these patients not well?

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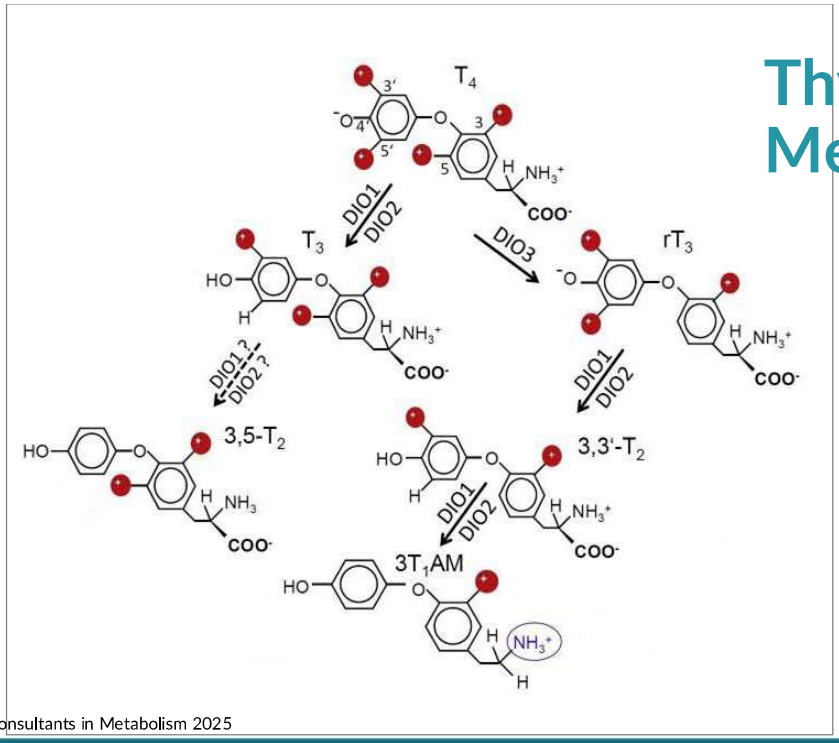

Thyroid Hormone Metabolites

From
22. Eur Thyroid J. 2019 Jun; 8(3): 115–129. The Colorful Diversity of Thyroid Hormone Metabolites (Josef Köhrle)

(Endotext: Peeters, Metabolism of Thyroid Hormone)

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T4 treated patients do not automatically have sufficient T3

NHANES population analysis (19)

- Euthyroid T4 users had higher serum total and free T4 and lower serum total and free T3 than healthy TSH matched controls. (23)
- 15–20% lower serum T3:T4 ratios in LT4 treatment (19, 24, 25)

Why? *High or fluctuating T4 leads to downregulation of peripheral T3 conversion. This is a common feature of Hashimoto's disease.*

- 80% of the T3 the body needs is converted in the target tissues (13)
- T3 conversion in the tissues declines in the presence of elevated serum T4
- T3 levels in the pituitary are relatively preserved

Quality of life is also worse in T4 treated euthyroid patients

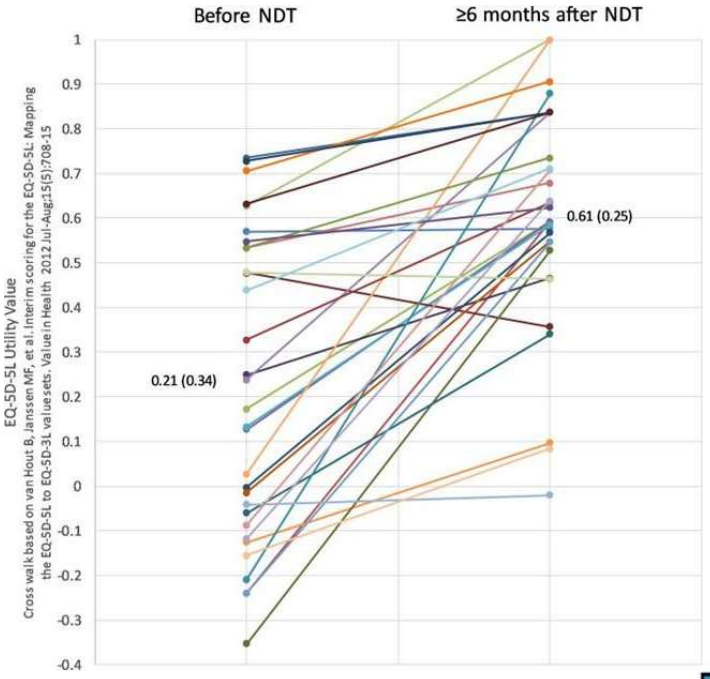
- 12-30% of chemically euthyroid T4 treated patients are symptomatic on QOL and thyroid specific instruments depending upon how measured *(4 Peterson) even if their TSH is 2.5 or less (26, 27)*
- In 2 crossover RCT's, 48% of subjects preferred T3 containing combinations (28, 29, 30)
- In the most symptomatic subgroups, outcomes were also significantly better on combination therapy (19 Hoang)

  Those who preferred NDT lost 4lb during the treatment; their subjective symptoms were significantly better while taking Dessicated Thyroid Extract (29, 31).

  - NDT- Extract made from pork (or sometimes beef) thyroid glands
  - 9 mcg of T3 for every 38 mcg of T4 in a 1"grain" tablet, usually 60 mg of extract.

QOL improvement after switch to NDT

- Selecting T4 “nonresponders” gives more dramatic results
- These patients have better outcomes when treated with Natural Dessicated Thyroid



From: 32. Heald AH, Premawardhana L, Taylor P, Okosieme O, Bangi T, Devine H, et al. Is there a role for natural desiccated thyroid in the treatment of levothyroxine unresponsive hypothyroidism? Results from a consecutive case series. *Int J Clin Pract* (2021) 75(12):e14967. doi: 10.1111/ijcp.14967

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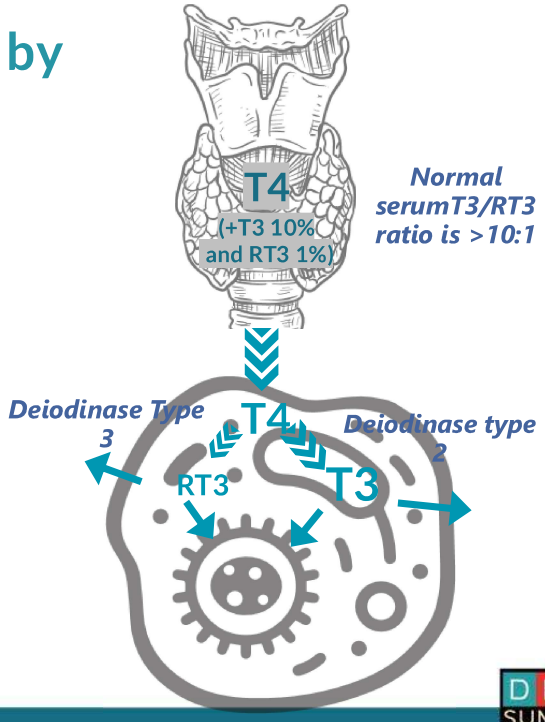
Activation of T4 is controlled by deiodinase enzymes

T4 is metabolized by deiodination to either T3 or RT3 (33)

- 5’ deiodinase type 2: main effector of tissue conversion of T4 to T3
- 5 Deiodinase type 3: main effector of diversion of T4 to Reverse T3, and breakdown of T3 to T2
- Deiodinase type 1: can do either depending on local environment, clears RT3 from circulation
- Reverse T3: Does NOT activate nuclear thyroid receptors, but has nongenomic functions that may downregulate Thyroid signaling (34)



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Deiodinase type 3 – by increasing RT3

- Prevents us from burning up our energy reserves during famines or illness
- Protects against excess T4 and T3 in hyperthyroid states
- In many pathologic conditions – increases the relative concentration of RT3 vs T3, a hypothyroid condition

*"Under chronic stress of all kinds, from injuries to infections, to low-temperatures, mental stress, to starvation – to transiently elevated serum T4 - Deiodinase 3 reduces thyroid signaling " (34)**

- **The balance of T3: RT3 is a proxy for the relative level of thyroid deiodinase activation vs inactivation and therefore thyroid function (1)**

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3 presentations with the same symptom pattern

- Overt hypothyroid patients –elevated TSH above 10 when not on treatment.

  Even when on guidelines based optimal T4 treatment, up to 30% of these will not be well.

- Patients with normal or nearly normal TSH (<10) with T4 in reference range - T3 can be low normal or frankly low.
  - These are the "Subclinical Hypothyroidism" group. Most of them have positive Hashimoto's antibodies and are nonresponsive to T4 therapy (27)

- Patients who have all labs within reference range - except RT3 and T3/RT3 ratio

Common denominator- symptomatic despite "normal" guidelines-based labs, but abnormalities in T3/RT3 balance (1)

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Who are these patients?
What factors favor conversion of T4 to Reverse T3?

- *Genetic Variations in deiodinases, transport proteins
  - SNP's in the genetic coding of the deiodinase-2 enzyme: Thr92Ala DIO2 present in 13% of the (British) population (36)
  - Potential to reduce T3 levels in many tissues, including the brain, by as much as 30% without affecting serum levels (37, 38)
- Medications: Amiodarone, Beta Blockers, PTU, others
- Liver/kidney dysfunction (lowers DIO1 clearance of RT3)
- Low Serum Iron (1)

More factors increase conversion of T4 to Reverse T3

- Diabetes
- Inflammation (cytokines, etc.)
- Cortisol deficiency (39)
- ***High or fluctuating levels of T4**: seen in Graves disease, Hashimoto's disease, once daily T4 dosing
- *Stress

These conditions collectively result in downregulation of thyroid action through a decreased ratio of T3 to RT3

*Stress dysregulates thyroid signaling in additive ways

Acute illness, injury, danger, mental stress, starvation: trigger 2 actions geared at energy conservation

- Chronic elevated cortisol levels suppress TSH via downregulation of the HPT axis
  Result is lower T3 ***and*** *T4 levels without a rise in TSH (40)*
  and
- T4 to active T3 conversion is selectively downregulated in favor of RT3

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Euthyroid Sick Syndrome - (E07.81)

- Also named **Non-Thyroidal Illness Syndrome -** these names imply the thyroid is functioning normally, only true in about 50% of cases (41)
- Reverse T3 has been most studied in critically ill patients:
  - In the ICU, a low T3/RT3 ratio has been found to be the single most predictive factor for mortality vs survival! (42)
  - Some reports indicate T3 infusions can stabilize some critically ill patients (post CABG) (43)
- *Frequently also found in Fibromyalgia, and Chronic Fatigue Syndrome. (44)
- It is also sometimes referred to as “Low T3 syndrome”, “Reverse T3 Syndrome”, or in the past, Wilson’s Temperature Syndrome

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Diagnosing ESS – add the T3/RT3 ratio

- Adding the TT3 and RT3 levels and Ratio gives us our diagnosis, and a guide for treatment - must be drawn together for a meaningful result.
  These are inexpensive and clinically available lab tests. ***Use code E07.81.***
- RT3 is only available as a Total number (free plus protein bound) (45)
  - RT3 alone is not useful for predicting clinical response
- We use the ratio of Total T3 to Reverse T3 to demonstrate either:
  Activation (towards T3) or
  Inactivation (towards Reverse T3)
- Drawn together, the TT3 /RT3 ratio >10:1 correlates quite well with whether a patient feels well or not.
- Free T3 and RT3 are not comparable*

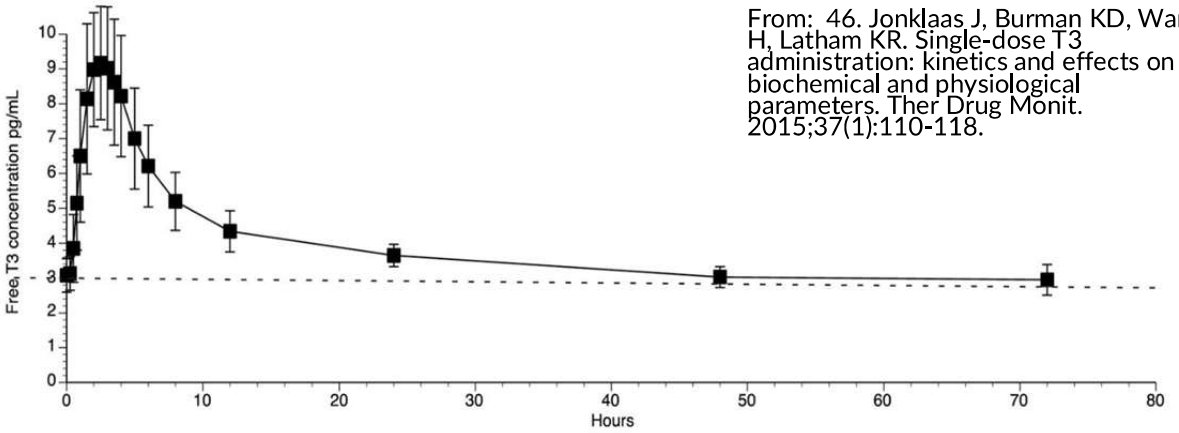
Thyroid Tests - Ideal vs Reference Ranges:

Reference ranges are broad! Ideal ranges are narrow.

Hormone	Ideal range	Reference Range (Labcorp)	
Free T4	0.7-1.0 (1.3)	.82-1.77	ng/dl
Free T3	3.4-4.0	2.0-4.4	pg/ml
Total T3	100-155	71-180	ng/dl
Reverse T3	8-14	9.2-24.1	ng/dl
Total T3 /RT3	10-14	None established	
TSH	0.4-1.0 (2.0)	.45-4.5	uIU/ml (31 Ito)

Actual Mean TSH is 1.4 ± 0.02 mIU/L (5, 6)

Treat the Adverse TT3/ RT3 ratio by adding T3



From: 46. Jonklaas J, Burman KD, Wang H, Latham KR. Single-dose T3 administration: kinetics and effects on biochemical and physiological parameters. Ther Drug Monit. 2015;37(1):110-118.

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Dividing the T4 dose can improve T3 suppression

Increased free T4 levels, as seen with levothyroxine therapy alone, appear to inhibit local deiodination to T3 ***except in the pituitary****, so that levothyroxine monotherapy may result in TSH inhibition while reducing T3 bioavailability in peripheral tissues. (47, 36, 48)*

- Half life of T4 is approx. 7 days (13)
- Once daily dosing results in a 25% higher serum level at Tmax (2-3 hours), than at steady state (49)
- With once daily dosing, T4 Levels remain elevated for up to 9 hours, with corresponding T3 and TSH suppression (50)
- Splitting the T4 dose can blunt this peak and attenuate the shift away from T3 and towards RT3(37)

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Lifestyle factors that improve thyroid signaling and T3 suppression

- Help patients manage their stress responses
- Address deficits: vitamins, minerals, protein
- Address food sensitivities that can cause inflammation and malabsorption
- Manage co-occurring medical conditions such as insulin resistance, adrenal insufficiency, and autoimmune inflammation
- Consider alternatives to beta blockers if indications permit

Your patients will be able to make lifestyle changes more easily once their thyroid imbalance/low energy levels, brain fog are addressed

Case Study – 31 year old Female

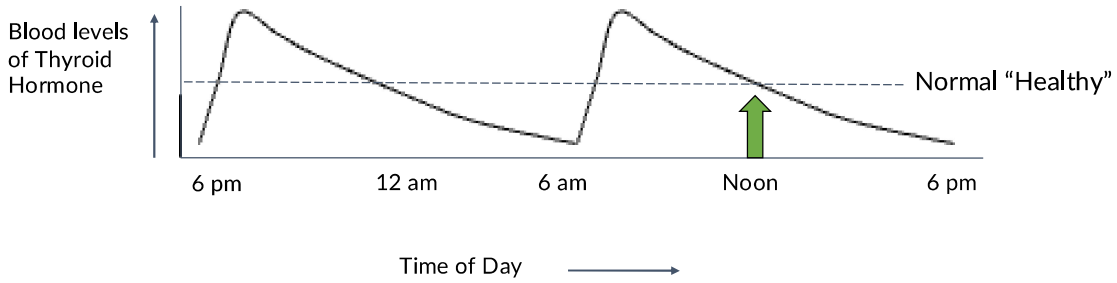
Hashimoto's diagnosis at age 17

- Symptomatic on Synthroid® 112 mcg q AM, despite Normal TSH and Free T4
- Symptoms:
  - Fatigue; feeling cold; cold hands & feet; tired on waking; gas & bloating; constipation; low mood; reduced libido and dry skin.
- 3 confirmed 1st trimester miscarriages in the past 2 years*
- Orthostatic lightheadedness and craving salt suggest adrenal issues
- Gluten-free diet (Dad has celiac)
- BMI 19.6.

Case Study – Hashimoto's disease

Initial recommendations

- Neonatal bovine "adrenal glandular" to mitigate adrenal symptoms.
- Asked her to divide her 112 mcg T4 dose to 56 mcg q 12h.*



Case Study – Initial Labs

Lab draw

- After 2 wks., blood was drawn 6 hrs. after AM dose:
  - TSH 0.663
  - fT4 1.66
  - fT3 2.9
  - tT3 87
  - RT3 36.1 H
  - Ratio tT3/ RT3 = 2.4 (L) (desirable= 12 +/- 2)

Case Study – Medication change

Next steps

- Replace some of her Levothyroxine with synthetic T3 – Liothyronine
- Gradual replacement is needed because of receptor upregulation
- Dosage "equivalency" 25 mcg of T4 = 5 mcg of T3
- For the first Month:
  - Prescribe Levothyroxine 25 mcg scored (breakable) tablets: enough to equal her current daily dose minus 12.5 mcg
  - Prescribe Liothyronine 5 mcg tablets enough for 15 mcg daily

Rx: _Synthroid (T4) 25 mcg tablets and Cytomel (T3) 5 mcg tablets

	Dose: AM		PM	Tablets:
Now on: T4 (Synthroid)	56 mcg	+	56 mcg	(112: ½ + ½)
Week	Go to:			
#1 T4	50 mcg	+	50 mcg	(2 + 2)
#1 T3	2.5 mcg	+	2.5 mcg	(½ + ½)
#2 T4	37.5 mcg	+	37.5 mcg	(1 ½ + 1 ½)
#2 T3	5 mcg	+	5 mcg	(1 + 1)
#3 T4	25 mcg	+	25 mcg	(1 + 1)
#3 T3	7.5 mcg	+	7.5 mcg	(1 ½ + 1 ½)
#4 T4	25 mcg	+	12.5 mcg	(1 + ½)
#4 T3	10 mcg	+	10 mcg	(2 + 2)

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T3 Dose Titration

- A written escalation schedule is essential
- Discuss dose and meal timing with the patient
- Liothyronine comes in 5mcg, 25mcg and 50 mcg.
- Patients should get in touch with any persistent adverse effect and back the dose down.
- Sometimes investigation and reeducation is needed!
- Frequent repetition of labs may be necessary

Liothyronine

Liothyronine 25 mcg

Liothyronine 5 mcg

Case Study – Hashimoto's disease

Follow up

- After 2 wks. on T4 25 + 12.5mcg & T3 10 + 10mcg, she felt much better, and her period had come on time for a change.
  - Increased energy, resolving brain fog, cold, and low mood, new hair growth*

- Blood drawn 6 hrs. after her Q 12h dose:
  - TSH 0.463
  - fT4 0.59 L
  - fT3 4.2
  - tT3 152
  - RT3 10.3
  - Ratio tT3/ RT3 = 14.8 up from 2.4 (desirable= 12 +/- 2)

Case Study Results

- We had to increase T4 – she was pregnant!
  - Binding proteins greatly increase with pregnancy...
  - In pregnancy, keeping FT4 at a higher level 1.0-1.2 is key
  - Q 4 week labs are required
  - RT3 should not be allowed to drift below 9.

- She delivered a healthy boy at full term.
- Meanwhile, she needed:
  - T4 37.5 + 37.5mcg and T3 10 + 10mcg

Treatment outcome

- After delivery her need for T4 decreased by about half
  - T4 25 +25mcg and T3 12.5 +10mcg
- Her T3/RT3 was stabilized at 11.4
  - FT4 at 0.8,
  - TSH at .71
  - Free T3 at 4.1
- Improved fertility
- Improved Libido*
- She feels well, with resolution of prior symptoms, and had a second successful non-assisted pregnancy

T3 Replacement- Treatment Pitfalls

Each hormone influences and modulates others. Thyroid is no exception.

- Cortisol and fatigue
- Insulin sensitivity
- Sex hormone changes
- Caffeine and stimulants
- Each person's ideal percentage of T3 to T4 will be different. There are different options for achieving that.
- Brand matters for T3 as well as T4

In Summary

- Hypothyroidism is a significant cause of poor outcomes and impaired QOL for our patients, regardless of biochemical euthyroid (TSH) status
- Standard methods of diagnosis miss 2 very important subtypes of thyroid dysfunction:
  - HPT axis suppression, and Non-Thyroidal Illness
- ***These patients are denied a diagnosis***

- Measuring the T3/RT3 Ratio and Free hormone levels in addition to TSH reveals these abnormalities
- Replacement with T3 or a properly balanced combinations of T4 to T3 can restore hypothyroid patients to health

Live Content Slide

When playing as a slideshow, this slide will display live content

Social Q&A for When "Normal TSH" Isn't Normal

QUESTIONS?

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