Optimizing Thyroid Function
A look at Reverse T3
The “brake pedal” of our Metabolism

American Academy of Anti-Aging Medicine
July 17, 2007

Riffat H. Qadir, MD, FACS, FAAOA
Canton, Ohio
Alan B McDaniel,MD,FAAOA, FAAEM
New Albany, IN
Louisville, KY

Optimizing Thyroid Function
Riffat H Qadir, MD

The following potential conflict of interest relationships are germane to my presentation.

Equipment: None
Speakers Bureau: None
Stock Shareholder: None
Grant/Research Support: None
Consultant: None

Status of FDA devices used for the material being presented
Not Applicable

Status of off-label use of devices, drugs or other materials that constitute the subject of this presentation
Reverse T3 Lab Test is run with non-FDA approved kit and is not to be used for diagnosis without confirmation by other medically established means.

Thyroid Physiology

HPT axis and feedback regulation

Key points:

- TSH regulates the thyroid gland, it has no other function.
- Thyroid hormone is made of two L-tyrosine molecules.
- Iodine is an essential component

Thyroid Physiology

Thyroid gland stores hormones bound to thyroglobulin;

-about 100 days' supply.

There are at least 4 hormone variants with some degree function, determined by iodine atoms
on the tyrosine (cyclic) rings.

- T4, T3, Reverse T3 and T2.

Thyroid Physiology

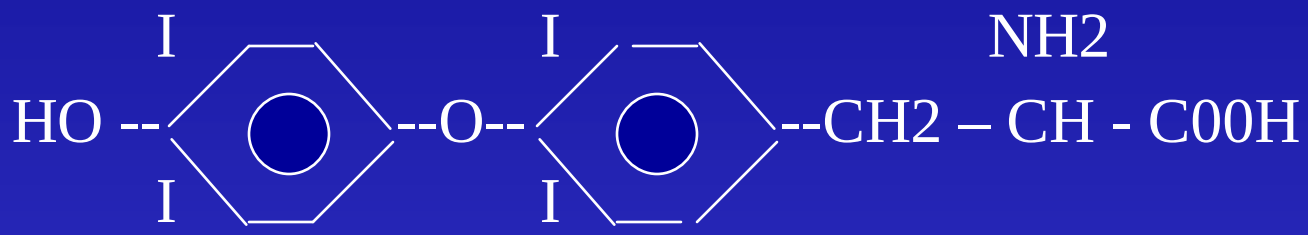
The positions of up to four iodine atoms determine the functions of these variants.

Iodine atoms on thyroid hormone are like the teeth of a key.

Thyroid Physiology

Graphic slide: Structure of T4.

T4:



Prime ring

.

Thyroid Physiology

The thyroid gland releases hormones when it is stimulated by TSH:

90% T4 - prehormone,
10% T3 - active hormone,
about 1% RT3
and a smidgen of T2

Blood levels are fairly constant, with minimal diurnal variation.

Thyroid Physiology

23% T3 produced in thyroid

2.5% Reverse T3 produced in thyroid

Remainder by peripheral conversion

Chopra IJ. *An Assessment of daily production and significance of thyroidal secretion of reverse T3 in man*. Clin Invest 1976;58:32-40

Thyroid Physiology

Thyroid hormone enters the cells,

- Stimulates the nuclear receptor,
- Regulates the rate of metabolism of virtually every cell and tissue.
-Non-genomic effects (esp. T4)

The thyroid gland is the thermostat for our metabolism.

Thyroid Physiology

Emphasis:

T4 has little function.

T3 is far more potent (at least 4x more).

Key:

T3 is the most active form of thyroid hormone

Thyroid Physiology

Circulating T3:

The thyroid makes little T3.

80% of T3 arises from T4,
by conversion in the cytoplasm
of peripheral tissues.

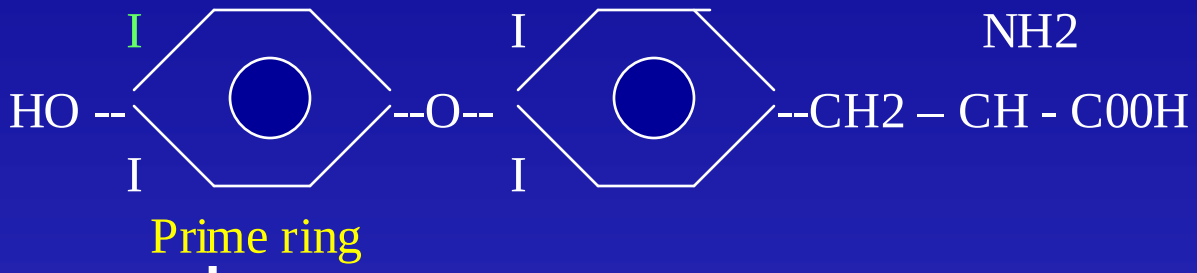
Enzyme: 5’ de-iodinase.

Snips off iodine from the 5’ locus
on the “outer” ring.

Thyroid Physiology

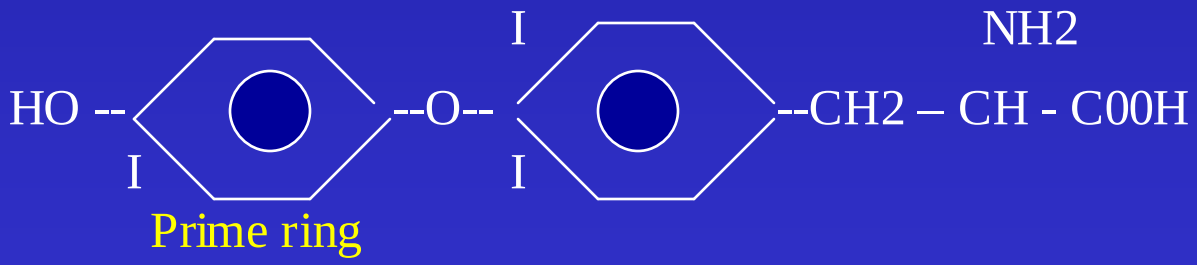
Graphic slide: T4 to T3.

T4:



5’ de-iodinase enzyme

T3:



Thyroid Physiology

New concept:

A third active hormone.

The body may not convert T4 to T3.

Reverse T3 (RT3)

may be made instead,

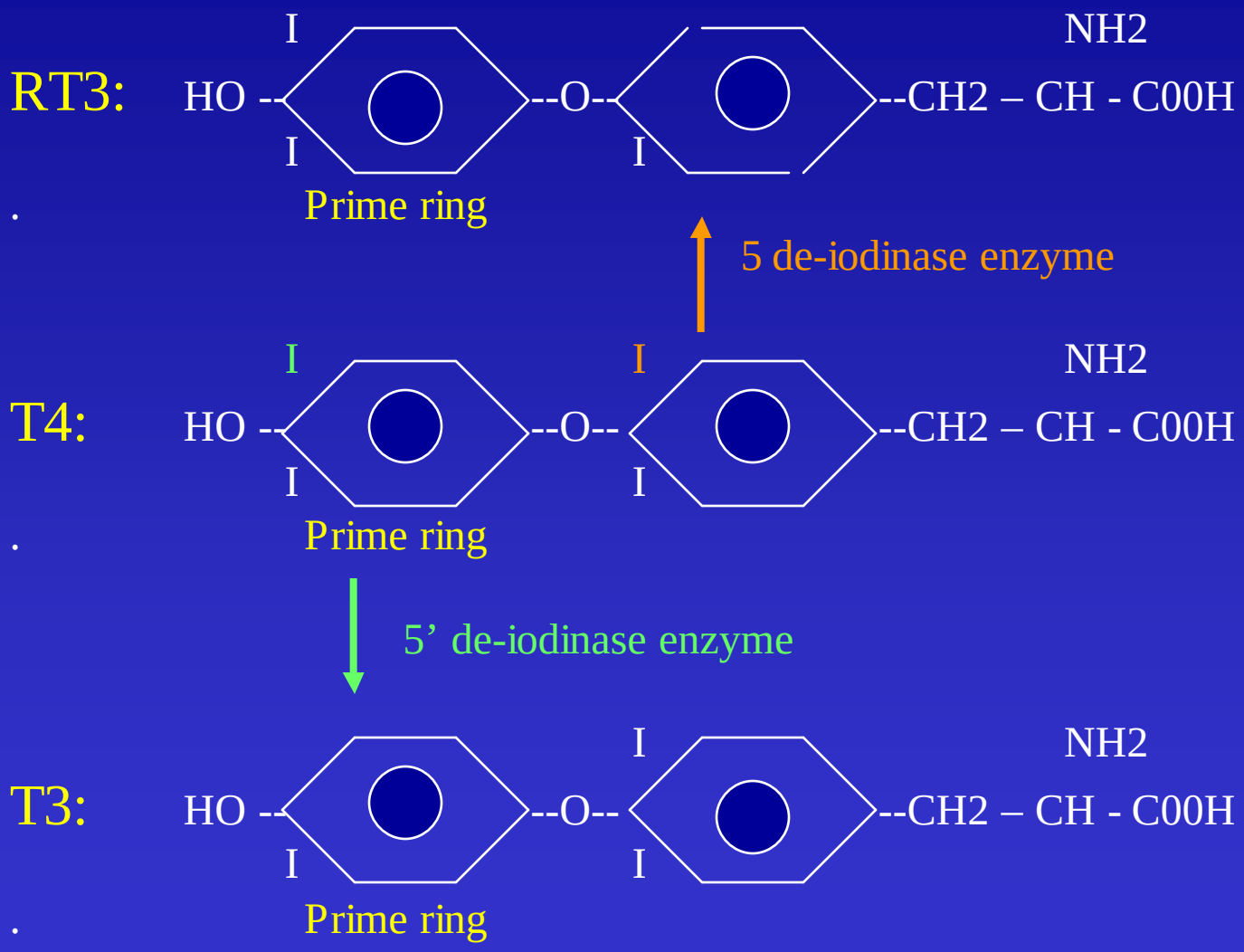
by removing the iodine from

the 5-locus on the inner ring.

Enzyme: 5 (not prime) de-iodinase.

Thyroid Physiology

Graphic slide: T4 into both T3 and RT3.



Physiology of Reverse T3

RT3 does not stimulate cell metabolism
as do T3 and even T4.

So: RT3 has been considered functionless.
An INACTIVE metabolite

NOTE:

The brake pedal doesn't make my car go faster,
but it certainly has a function.

Physiology of Reverse T3

RT3 appears to have
its own receptor on
the nuclear membrane.

The obvious reason
would be that
it has a function there.

Physiology of Reverse T3
Reverse T3 has its own Receptor

- Kobayashi A. *Nuclear binding sites for Reverse T3 in human placenta.* Osaka City Med J 1989;35:137-144.
- Dozin R. *Nuclear binding of T3 and T4 interaction with Reverse T3: evidence for an additional binding site for thyroid hormone.* In The Low T3 Syndrome, Ed.:RD Hesch, pp101-104, Academic Press, London
- Smith HC. (1980) *Evidence for a second nuclear binding site for thyroid hormones. Binding of Reverse T3 to hepatic nuclear protein and regulation by thiol active agents.* In Thyroid Research. Eds. JR Stockigt, S Negataki, vol. V111, p 286. Australian Academy of Sciences, Canberra.
- Wersinga WM. (1982) *Specific nuclear binding sites of T3 and Reverse T3 in rat and pork liver: similarities and discrepencies.* Endocrinology, 110, 2052-2058.

Physiology of Reverse T3

Reverse T3
inhibits thyroid function.

Many research studies
support this idea.

Physiology of Reverse T3

Reverse T3 Inhibits Thyroid Function

Friberg L. *Association between Increased Levels of Reverse T3 and Mortality after Acute Myocardial Infarction*. The American Journal of Medicine. 2001;111:699-702.

"It is not evident why it is Reverse T3 and not T3 itself that is of prognostic importance. This suggests the possibility that Reverse T3 might have biological activities, perhaps acting as a competative inhibitor that disrupts the T3 signaling… Determination of Reverse T3 in patients with myocardial infarction is a simple way to identify high-risk patients."

Physiology of Reverse T3

Reverse T3 Inhibits Thyroid Function

St. Germain DL. *Metabolic Effect of reverse T3 in Cultured Growth Hormone-producing Rat Pituitary Tumor Cell.* J Clin Invest. Aug 1985;76:890-893.

"These findings suggest that the control of T4 to T3 conversion by thyroid hormones in the anterior pituitary gland is mediated by a unique cellular mechanism independent of the nuclear T3 receptor, and reverse T3 may play a regulatory role in controlling this enzymatic process."

Physiology of Reverse T3
Reverse T3 Inhibits Thyroid Function

Kaiser, CA. *In vivo Inhibition of the 5' Deiodinase Type II in Brain Cortex and Pituitary by Reverse T3.* Endocrinology Aug 1986;119(2):762-70.

"We therefore conclude that Reverse T3 inhibits 5'D-II in brain cortex per se independently of T4."

This leads to a reduction in T3 levels and therefore a reduction in thyroid function.

Physiology of Reverse T3
Reverse T3 Inhibits Thyroid Function

Szymanski PT. *Effects of thyroid hormones and reverse T3 pretreatment on beta-adrenoreceptors in the rat heart*. Acta Physiol Pol 1986;37:131-138.

"Hypothyroidism decreased maximal binding capacity value (of *B*-adrenergic antagonist hydroxybenzylpindolol), but increased the affinity of *B*-adrenoreceptors. Pretreatment of rats with Reverse T3 produced changes in *B*-adrenoreceptors similar to those seen in hypothyroid rats."

Physiology of Reverse T3

Reverse T3 Inhibits Thyroid Function

duPont JS. *Is reverse T3 a physiological nonactive competitor for the action of T3 upon the electrical properties of GH3 cells?* Neuroendocrinology 1991;54:146-150.

"When a cell was beforehand superfused with Reverse T3, the effect of T3 was prevented…The prevention of the effect of T3 by Reverse T3 might have a biological significance. In hyperthyroidism the levels of Reverse T3 and T3 are both increased and the higher Reverse T3 level could mitigate the influence of T3. In contrast, in hypothyroidism both Reverse T3 and T3 levels are decreased, and in spite of a lowered T3 level, the action of T3 would then be more pronounced."

Physiology of Reverse T3

Reverse T3 Inhibits Thyroid Function

McCormack PD. *Cold stress, reverse T3 and lymphocyte function.* Alaska Med 1998;40(3):55-62.

"There was an indication that lymphocyte function is depressed by increasing serum concentration of Reverse T3."

Physiology of Reverse T3
Key Concepts

The fate of T4 determines the rate of metabolism:

- If T4 is converted to T3, metabolism is increased.
- If T4 is converted to RT3, the rate of metabolism is reduced.
- If T4 is conjugated, nothing changes.

Physiology of Reverse T3

Using a business metaphor to explain:

In the economy of our body:

- T4 is billing – a potential for money;
- T3 is collections – money received;
- RT3 is overhead expense – money lost.

Physiology of Reverse T3

To run a healthy practice,

- Our collections must sufficiently exceed our expenses.

For a healthy metabolism,

- T3 must exceed RT3.

Physiology of Reverse T3

Another metaphor for T3 and RT3:

Race car drivers drive with “both feet,”

- one foot on the gas and
- one foot on the brake.

How fast the car goes depends on the amount of each stimulus.

The thyroid does the same thing:

- T3 is the gas,
- RT3 the brake.

Physiology of Reverse T3

RT3 rises in response to Stress.

- Physiological: Hypothermia and starvation
- Psychological: Students during exams and patients entering the O.R.
- Physical: Injury, MI, cancer, CHF, and ICU population.

Kvetny J. *Thyroxine binding and cellular metabolism of thyroxine in mononuclear blood cells from patients with anorexia nervosa.* J Endocrinol 1983;98:343-350.

Scriba PC. *Effects of obesity, total fasting and realimentation on T4, T3, TBG, transferrin, alpha 2 haptoglobin, and C3 in serum.* Acta Endocrinol (Copenh) 1979;91:629-643.

Cortisol

from James Paoletti RPh

- Excess
  - Inhibits T4 to T3 conversion
  - Suppresses TSH
  - Decreases thyroid receptor responsiveness
- Deficiency
  - Decreases thyroid receptor responsiveness
  - May inhibit T4 to T3 conversion
  - Regulates T3 receptor density
  - Modifies hormone transport across cell membrane

Physiology of Reverse T3

Reverse T3 reduces the metabolic rate

- as an adaptive response
- during times of stress

(Injury, illness or starvation).

Remember:

Adaptive responses may become maladaptive if continued too long.

Physiology of Reverse T3

In our experience,

every patient with elevated T4 blood levels has robust RT3 levels,

- whether from Graves' disease,
- excessive treatment with synthetic T4 or
- excessive treatment with USP

  "Armour" thyroid.

Physiology of Reverse T3

For this reason:

We believe that RT3 also serves as an adaptive response to protect the individual from excessive thyroid hormone levels.

Physiology of Reverse T3

Reverse T3 Inhibits Thyroid Function

duPont JS. *Is reverse T3 a physiological nonactive competitor for the action of T3 upon the electrical properties of GH3 cells?* Neuroendocrinology 1991;54:146-150.

"When a cell was beforehand superfused with Reverse T3, the effect of T3 was prevented…The prevention of the effect of T3 by Reverse T3 might have a biological significance. In hyperthyroidism the levels of Reverse T3 and T3 are both increased and the higher Reverse T3 level could mitigate the influence of T3. In contrast, in hypothyroidism both Reverse T3 and T3 levels are decreased, and in spite of a lowered T3 level, the action of T3 would then be more pronounced."

Physiology of Reverse T3

T3 is inactivated to T2 (3',3 T2)

by the 5 de-iodinase enzyme.

(5 DI)

RT3 is inactivated to T2 (3',3T2)

by the 5' de-iodinase enzyme.

(5' DI)

So, each enzyme plays a double role.

Physiology of Reverse T3

5’ de-iodinase makes T3 and destroys RT3.

5 de-iodinase makes RT3 and destroys T3.

Malfunction of just one enzyme effects levels of both T3 and RT3.

Effects are amplified by double roles.

Physiology of Reverse T3

Furthermore,

RT3 inhibits 5’ de-iodinase and impairs T4 to T3 conversion, thus inhibiting thyroid function.

St. Germain DL. *Metabolic Effect of reverse T3 in Cultured Growth Hormone-producing Rat Pituitary Tumor Cells.* J Clin Invest Aug 1985;76:890-893.

Kaiser, CA. *In vivo inhibition of the 5’Deiodinase Type II in Brain Cortex and Pituitary by Reverse T3.* Endocrinology Aug 1986;119(2):762-70.

Physiology of Reverse T3

There are isoforms of 5' de-iodinase (5'-DI) enzyme with functional implications.

The 5'-DI isoform in somatic cells (liver, kidney, etc) is dependent upon the trace metal selenium.

The 5'-DI isoform in cells of the CNS, (including hypothalamus and pituitary) is not dependent upon selenium.

Physiology of Reverse T3

It may be significant that the CNS has
a more "reliable" form of 5'-DI that would

- allow the brain an adequate T3 supply
- even if the body is deficient.

Speculation:

Tests of the HPT axis (TSH and T4)
may not be effected by selenium deficiency

Physiology of Reverse T3

Of further interest,

The 5 de-iodinase (5-DI) enzyme is not effected by selenium deficiency.

Production of RT3 is increased during starvation and malnutrition,

while T3 levels fall.

Physiology of Reverse T3

Many nutrients are involved in the production of T3

Bottom line:

During times of starvation and malnutrition, stress and injury, many mechanisms may

- reduce T3
- and allow increased RT3 production

NET: Reduced energy consumption/metabolism and inability of standard testing methods to detect a problem.

Laboratory Assessment

DIAGNOSIS: The laboratory work-up.

Test five hormones: Production & processing!

- TSH, freeT4 (fT4), freeT3 (fT3),
  RT3 and totalT3 (tT3).

FreeT3 is most accurate measure of T3

but

RT3is available only as a total measure,

- so we need total T3 for comparison.

Reverse T3

Lab disclaimer:

"This test was performed using a kit that has not been cleared or approved by the FDA. The analytical performance characteristics of this test have been determined by (lab name). This test should not be used for diagnosis without confirmation by other medically established means."

Laboratory Assessment

So, what is “normal RT3” and how do we figure?

Thyroid production of RT3:

Endo. texts state: The thyroid gland releases

90% T4, 10% T3 and ~ 1% RT3

Starting out, the body is given T3/RT3 ratio = 10.

Laboratory Assessment

Using a crude statistical method,

Compare "normal" RT3 to total T3 (tT3).

Both are "total" measures.

tT3: reference range = 85 – 205ng/dL

RT3: reference range = 90 – 350pg/mL

Corrected for units, RT3 is 9 – 35ng/dL.

The ratios of tT3 to RT3 are:

- Low end: tT3/RT3 = $85_{ng/dL}/9_{ng/dL}$ = 9.4
- High end: tT3/RT3 = $205_{ng/dL}/35_{ng/dL}$ = 5.9

Laboratory Assessment

If the reference intervals are on target,

normal tT3/RT3 runs 6 - 10.

We have been watching these ratios for a few years,

pre and post-treatment.

We find that patients who respond well to treatment - and particularly those who need supplementary T3 - feel best when their tT3/RT3 ratio is 12 +/-2.

Laboratory Assessment

Impression:

Extremes of age must be considered individually.

But ages from the teens through the70’s seem to hold true to the rule of 12 +/- 2.

Laboratory Assessment

Optimal hormone balance debatable:

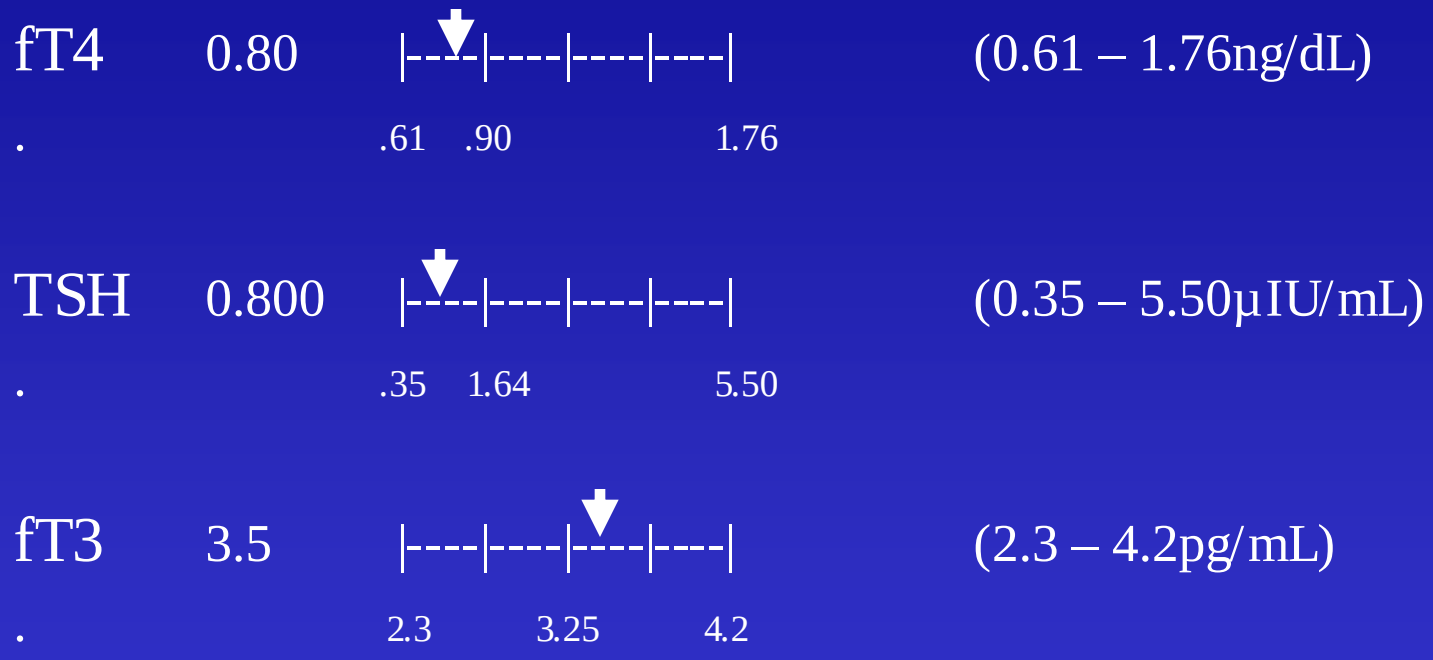
Our observations:

Patients (not well people) treated with T4 and T3 seem to do best with:

- TSH around 0.7 – 0.9μIU/mL.
- FreeT4 around 0.7 – 0.8ng/dL.
- FreeT3 optimally 3.4 – 3.7pg/mL.
- TotalT3/RT3 ratio 12 +/-2.

Laboratory Assessment

Graphic slide: “Ideal” thyroid values graphed.



NB: “Normal range” is not ideal range,
- even normalcy is debatable.

Laboratory Assessment

Test autoantibodies:

TPO-Ab: Most commonly positive Ab.

Tg-Ab: Worth testing despite one report.

- Up to 10% of our cases show only Tg-Ab positive.
- And it seems useful to predict autonomous function.

Laboratory Assessment

Two tests for TSH receptor Ab's.

TR-Ab: Radio-immune assay for

- both stimulating and blocking Ab's.

TSI is bio-assay as patient's serum is

- placed over a cell culture.

TSI report: Effects on cell activity as a percentage.

- Used only for stimulating-Ab (Norm. < 130%)
- No data on results with reduced function.

Suboptimal Thyroid Function

Courtesy of James Paoletti

- A number of situations can contribute
  - Inadequate production of T4
  - Poor conversion from T4 to T3
  - Problems with the cell's ability to take up T3
  - Problems with receptor function (Vitamin D deficiency)
  - Problems with intracellular transport (low ferritin)

Hypothyroidism

HYPOTHYROIDISM:

Most important abnormal findings:

- Elevated TSH (duh!) and
- low free T3.

Most common abnormal finding:

- low tT3/RT3 ratio

  which is also very important as the most often ignored abnormality.

Hypothyroidism

"Classical" hypothyroidism:

- Symptomatic patient
- Abnormal gland on PE
- Abnormal laboratory tests:

    Elevated TSH

    Low freeT4.

Hypothyroidism

Classical treatment:

Synthetic T4.

- Introduced in late 50's.
- Successfully marketed.
- Depends on peripheral de-iodination for optimal function.

Hypothyroidism

I think that we are all familiar with the standard recommendations for treatment with synthetic T4, yet many patients on T4 remain tired and cold intolerant.

Let's investigate possible problems with this strategy.

Hypothyroidism

Common patient problems with T4 treatment:

(Series of over 200 cases- tested at mid-dose)

1. Insufficient replacement
   - Elevated TSH
2. Excessive replacement
   - Low TSH and high T4
3. Inappropriate metabolism of T4
   - Low T3
   - T3 - RT3 imbalance

Hypothyroidism

Find the cause of treatment failure:

Test all five hormones

TSH, fT4, fT3, RT3 and tT3

Draw blood at mid-dose

to avoid confusion about

peak and trough levels.

Hypothyroidism

Consider Pharmacokinetics:

Pills dissolve in stomach,

- hormones absorbed from intestine,
- make a first pass through the liver,
- then enter the systemic circulation.

Cleared from blood by liver and kidney

- no significant entero-hepatic circulation.

Hypothyroidism

Peak and trough dynamics

of thyroid hormone are not well defined,

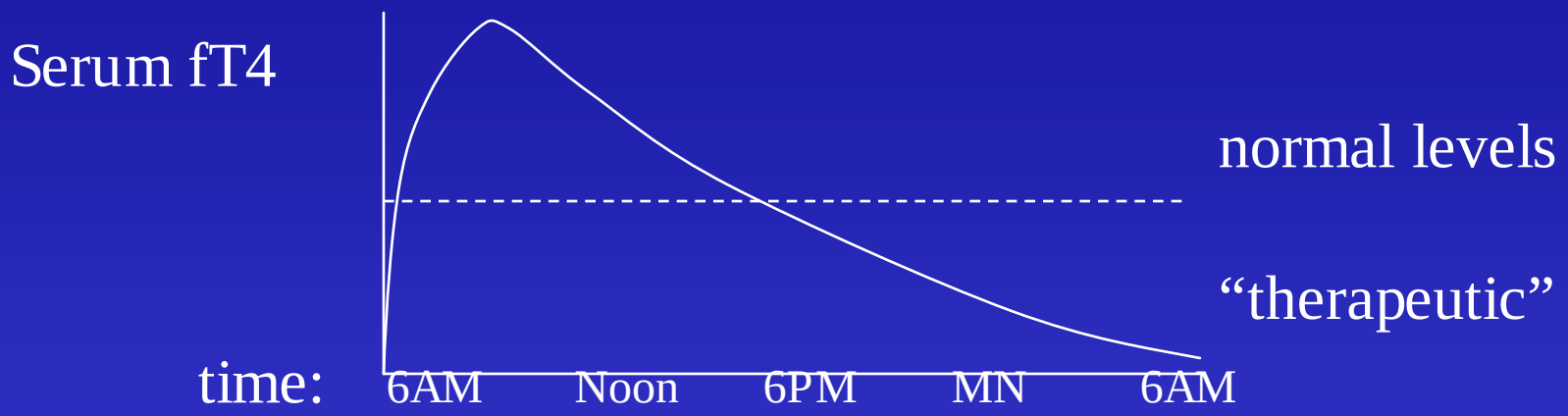
- compared to gentamycin, for example.

We believe this is because thyroid hormone has been in use long before either

- such concepts were commonplace
- or the technology existed to perform the tests.

Hypothyroidism

Graphic slide: Peak and trough levels of T4.



bottom line: Peak and trough levels matter.

Hypothyroidism

When should we test blood: Peak or trough?

- Some physicians test trough levels.
- Most physicians test randomly.

Most patients take T4 every AM,

have blood drawn

- on the way to work
- or at lunch break.

Hypothyroidism

Heard at AAEM meeting:

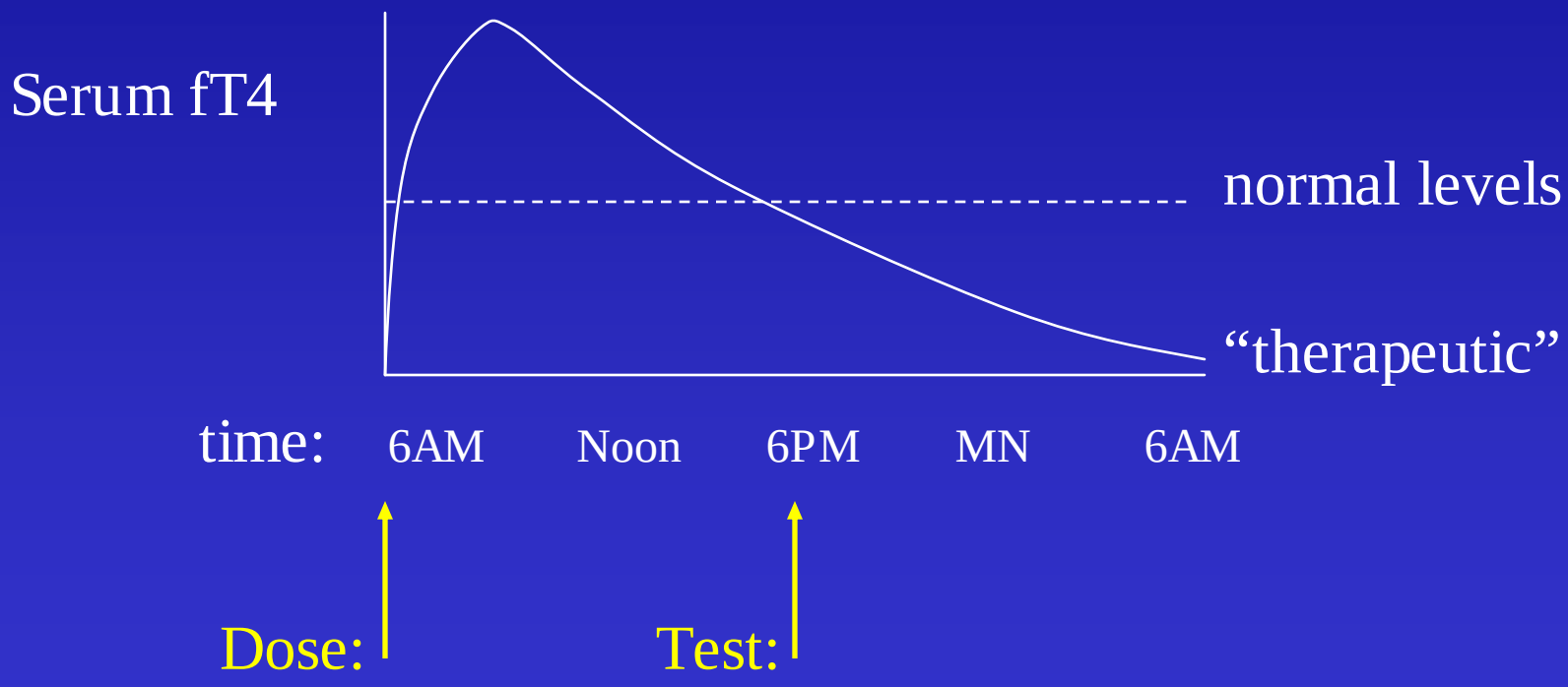
"Draw blood at mid-dose."

- Test neither peak nor trough, since pharmacokinetics are not well defined.

- Blood at mid-dose gives an average level,
  half the day higher,
  half the day lower.

Hypothyroidism

Graphic slide: Peak and trough levels of T4.



Hypothyroidism

Despite PDR statement that

half-life of T4 is 9 – 10 days in hypothyroid patients,

many patients tested at mid-dose

have elevated TSH,

- even though their previous test results showed normal TSH levels.

Hypothyroidism

What if:

T4 cannot be activated into T3?

Patients have:

- normal TSH levels,
- normal T4 levels but
- low T3 and interestingly,
- elevated RT3.

Hypothyroidism

Giving patients T4 without checking their ability to convert T4 into T3

is like

sending cans of food to starving children without asking whether they have a can-opener.

Factors That Inhibit T4 to T3 Conversion

Courtesy of James Paoletti RPh

- Stress – excessive cortisol
- Inadequate production of adrenal hormones
- Halogen toxicity
- Excess reverse T3
- Estrogen
- Obesity
- Liver and kidney disease
- Starvation

Factors That Inhibit T4 to T3 Conversion

Nutrient Deficiencies

- Selenium
- Chromium
- Iron
- Vitamin A
- Vitamin B6
- Vitamin E
- Zinc
- Iodine
- Copper
- Vitamin B2
- Vitamin B12

Factors That Inhibit T4 to T3 Conversion

Courtesy of James Paoletti RPh

Medications

- Glucocorticoids
- Beta Blockers
- Birth Control Pills
- Estrogen replacement
- Estrogen dominance
- Lithium
- Iodinated Contrast
- SSRI's
- Opiates
- Phenytoin
- Chemotherapy
- Theophyline
- Fluoride suppl

Hypothyroidism

In our experience:

The excessive conversion of T4 to RT3 is

-the most common cause of failure of "classical" thyroid treatment with synthetic T4

- more common than the low production of T3.

The amount of T3 produced, even though "normal," is inadequate to overcome the inhibitory effects of RT3.

Thyroid Hormone Replacement

Alternatives to treatment with T4:

- "Ready-made" mixtures of T4 and T3.
  - USP "Armour" thyroid (Forrest), pork.

    60mg = T4 38mcg + T3 9mcg
  - Thyrolar (Forrest), synthetic bio-identical.

    60mg = T4 50mcg + T3 12.5mcg

  Both give 80% T4 and 20% T3.

- T3 only.
  - Cytomel (King): Synthetic bio-identical.

Thyroid Hormone Replacement

Life according to PDR

T4

½ life: 9-10 days

Dosage: 50 – 200 mcg d

T3

½ life: 1.4 days

Dosage: 25 – 75 mcg d

Thyroid Hormone Replacement

Our Experience

BID Dosing gives far better results

Thyroid Hormone Replacement

USP desiccated thyroid: Advantages:

- It gives similar T3 to a normal human thyroid gland.

  USP 20% T3 vs. human 23% T3

- Cheap, available and popular: “a classic.”
- Some attribute merit to intrinsic glandular elements, perhaps calcitonin.

Thyroid Hormone Replacement

USP desiccated thyroid: Disadvantages:

- Best dosing is Q12h (short half-life T3).
- All other physicians try to replace it.
- Pork source is unacceptable for:

  The scrupulously religious

  Patients allergic to pork.

Thyroid Hormone Replacement

USP desiccated thyroid: Disadvantages:

- Best dosing often requires taking multiple pills (no 45mg or 75mg tablets).
- The pills stink (from calcitonin).
- Patients may need more T3 than 20%.
- Antigens in the desiccated glandular may inflame AIT patients' glands.

Thyroid Hormone Replacement

Thyrolar: Advantages:

- It gives similar T3 to a normal human thyroid gland.

  USP 20% T3 vs. human 23% T3.

- "Bio-identical synthetic" reassures some.
- Other physicians generally accept it.
- No pork or gland antigens; Useful for:

  The scrupulously religious

  Patients allergic to pork.

Thyroid Hormone Replacement

Thyrolar: Disadvantages:

- Best dosing is Q12h (short half-life T3).
- Expensive and rarely covered on “plan.”
- Must be kept refrigerated.
- Best dosing often requires taking multiple pills (no 45mg or 75mg tabs).
- Patients may need more T3 than 20%.

Thyroid Hormone Replacement

Synthetic T3 (Cytomel): Advantages:

* Tx success not dependent on T4 conversion.

Treat with active thyroid hormone:

- Corrects T3/RT3 imbalances
- More acceptable to other physicians

  discussed in recent medical literature.
- Biologically identical
- Synthetic: No concerns for the religious.

Thyroid Hormone Replacement

Synthetic T3: Disadvantages:

- Short half-life requires Q12h dosing (Q8h?)
- Inconsistency in compounded encapsulations.
- Expensive and not on all “plans.”
- Often have to break pills for best dose.
- Not used alone for suppressive treatment, which requires T4 also.

Thyroid Hormone Replacement

Studies comparing T4 vs T4/T3 Replacement

- No objective advantage of combination
- Patients still prefer combination
- Dose of T3 generally inadequate
- Once daily dosing of T4 and T3

Thyroid Hormone Replacement

T4 vs T4/T3

Saravanan P. *Thyroid Hormone Profiles on Combined T3/T4 Therapy*. Exp Clin Endocrinol Diabetes 2007;115:261-267.

Escobar-Morreale H. *Thyroid Hormone Replacement Therapy in Primary Hypothyroidism: A Randomized Trial Comparing T4 plus T3 with T4 alone*. Annals of Internal Medicine. March 2005;142(6);412-424.

Siegmund W. *Replacement Therapy with T4 plus T3 (14:1) is not superior to T4 alone to improve well-being and cognitive performance in hypothyroidism.* Clin Endocrinology 2004;60:750-757.

Fadeyev V. *TSH and thyroid hormones concentrations in patients with hypothyroidism receiving therapy with T4 alone or in combination with T3.* Hormones 2005;4(2):101-107.

Thyroid Hormone Replacement

Our experience:

- Treatment with T4 alone rarely optimal,

  though Q12h dosing works better.
- Treatment with T4+T3 pre-mix works better,

  though not always optimally.
- Many patients need “richer” mix of T4/T3

  than offered in the pre-mixes:

  70/30, 60/40 - even 50/50.

Thyroid Hormone Replacement

How to choose? Here are a few suggestions:

Patients well-suited for T4+T3 mix:

- Profoundly hypothyroid:
  - Post-ablative (131-I) or
  - Surgically hypothyroid or
  - Severely elevated TSH.
- Patients who need suppressive Tx:
  - Big goiter
  - Autoimmune thyroiditis.

Thyroid Hormone Replacement

Patients suited for T3 treatment:

(This is all controversial!)

- Mild hypothyroidism with poor T3/RT3,
- Autoimmunity with poor T3/RT3 ratio,
- Poor response to T4 treatment alone.
- Low-T3 or “euthyroid sick” syndrome.

Low Functional Effect

T3 and RT3 imbalance:

Syndrome synonyms:

- Low T3 syndrome;
- Euthyroid sick syndrome;
- Non-thyroidal illness;

What's up with this?

T3 and RT3 Imbalance

Recall the history and physiology of RT3.

Once believed meaningless,

RT3 is an inhibitor of T3 action.

In response to stress,

- T3 production is decreased and
- RT3 production is increased.

Whether from lowered T3,

increased RT3 or both,

- the patient effectively has low-T3.

T3 and RT3 Imbalance

When a patient has maladaptive low-T3 effect

- but his thyroid gland is not diseased,
- his condition is most often called:

"Low T3 Syndrome" (LT3S) or
"Euthyroid Sick Syndrome" (ESS)

Critically ill patients are usually studied.

T3 and RT3 Imbalance

There are many causes of ESS:

Effects of Stress, Drugs and Cytokines on:

- Hypothalamus
- Pituitary
- Peripheral conversion

T3 and RT3 imbalance seems the key:

* It is uniformly agreed that low T3 and high RT3 indicate poor prognosis.

*T3 Rx improves prognosis

Low T3 and High RT3 indicate Poor prognosis

Schulte C. *Low T3 syndrome and nutritional status as prognostic factors in patients undergoing bone marrow transplantation.* Bone Marrow Transplant 1998;22:1171-1178.

"All patients experienced a significant decrease of transferrin and T3, accompanied by an increase of Reverse T3 and Reverse T3/T3 ratio at day 14 after BMT. At day 28 after BMT, patients (that survived greater than one year) showed recovery from these changes with an increase of transferrin and a fall in Reverse T3 and the Reverse T3/T3 ratio, which was not seen in patients who died."

Low T3 and High RT3 indicate Poor prognosis

Peeters RP. *Serum reverse T3 and T3/reverse T3 are prognostic markers in critically ill patients and are associated with postmortem tissue deiodinase activities.* J Clin Endocrinol Metab Aug 2005;90(8):4559-65.

"In critically ill patients who required more than 5 days of intensive care, Reverse T3 and T3/Reverse T3 were already prognostic for survival on day 1. On day 5, T4, T3, but also TSH levels are higher in patients who will survive."

Low T3 and High RT3 indicate Poor prognosis

Friberg L. *Association between Increased Levels of Reverse T3 and Mortality after Acute Myocardial Infarction.* The American Journal of Medicine 2001;111:699-703.

"Determination of Reverse T3 levels may be a valuable and simple aid to improve identification of patients with myocardial infarction who are at high risk of subsequent mortality."

T3 Replacement Improves Outcome

Pingitore A. *Acute Effects of T3 Replacement Therapy in Patients with Chronic Heart Failure and Low T3 syndrome: A Randomized, Placebo Controlled Study*. J Clin Endocrin Metab. First published ahead of print January 2, 2008 as doi:10.1210/jc.2007-2210.

"In dilated cardiomyopathy patients short-term synthetic T3 replacement therapy significantly improved neuroendocrine profile and ventricular performance."

T3 Replacement Improves Outcome

Yuan X-Q. *T3 Antagonizes Adverse Effects of High Circulating RT3 During Hemorrhagic Shock*. The American Surgeon 1988;54(12):720-725.

"In the untreated group, 8 of 10 dogs (80%) died during uncompensated shock, in comparison to 3 of 11 dogs (27%) that received T3."

T3 and RT3 Imbalance

Most authors focus on low T3.

Some study levels of RT3.

- Few compare the T3/RT3 ratio.

In our experience, the best measure of thyroid functional status is the ratio of tT3 to RT3.

T3 and RT3 Imbalance

PROPOSAL:

Euthyroid sick syndrome is caused by

excessive RT3 compared to T3;

and exists in a milder form

- that commonly causes chronic fatigue
- and symptoms of hypothyroidism.

T3 and RT3 Imbalance

This simple concept has been overlooked because of :

- first, disregard of RT3 function and
- secondly, dogma that T4 will always be converted adequately to T3.

T3 and RT3 Imbalance

How do patients with this problem present?

Unexplained chronic fatigue, including:

- Poor response to T4 treatment of hypothyroidism;
- Chronic fatigue syndrome;
- Obesity and insulin resistance;

T3 and RT3 Imbalance

How do they present?

They may have histories of:

- Chronic situational stress
- Eating disorders
- Over-trained athlete syndrome

T3 and RT3 Imbalance

How do they present?

They may take drugs that
inhibit T4 to T3 conversion :

- Steroids,
- beta-blockers,
- amiodarone (Cardura) and
- PTU, but not Tapazole.

T3 and RT3 Imbalance

Diagnosis:

- History, physical exam and basal temps are useful.
- Perform complete thyroid lab evaluation, and check the total T3 to RT3 ratio.

* Less than 10 usually means a problem.

T3 and RT3 Imbalance

Once the diagnosis is evident, it is well to:

- Educate the patient

  about thyroid physiology
- Explain the problem -

  can use a videotape.
- Explain why other doctors told them

  their tests were normal.

T3 and RT3 Imbalance

Review their treatment options,

based upon known causes of increased RT3.

Reduce your stress:

- Sleep at least 8hrs a night.
- Exercise 30min/day x 5d/wk.

Gently: Yoga or walking.

- Meditation or prayers (Kabat-Zinn).

T3 and RT3 Imbalance

Correct Adrenal prior to Thyroid

Improve your response to stress:

Adrenal nutrition.

- Adrenal “glandular” AM and HS,
  Sometimes at noon, too.
- Pregnenolone/progesterone
  for the ladies.
- DHEA for the gents.
  Also dosed AM and HS.

Build these slowly

T3 and RT3 Imbalance

Diet: Keep your blood sugar levels steady.

- Avoid sugar and starches.
- Avoid preserved & processed fruit.
- Avoid sweeteners, fructose and sucralose.

Eat meat, vegetables and whole grains.

T3 and RT3 Imbalance

Supplement the ability to convert T4 to T3.

Pre-mixed supplements are available.

Ashwaganda?

T3 and RT3 Imbalance

If the patient is taking Q day synthetic T4:

Divide the dose to Q 12hrs.

This may reduce RT3 production:

- RT3 is increased in hyperthyroidism, so the

- big peak of once-daily dosing may increase RT3.

Consider T3 +/- T4 treatment

T3 and RT3 Imbalance

Treatment trial on T3/T4

- Make sure the patient knows
  this is not the standard of practice
  in your community –

In Summary

- Test 5 hormones: TSH, fT4, fT3, tT3, RT3
- Draw blood at mid-dose
- BID dosing, especially T3

Thank You Alan!

McDaniel AB. *Chronic Fatigue Syndrome.* In Krouse, Chadwick, et al. ed. *Allergy and Immunology. Philadelphia: Lippincott Williams and Wilkins, 2002:346-382.*