

Controversies in Thyroid Disease

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Conflicts of Interest/Declarations

- I have no financial interest in, and take no fees or funding from, any pharmaceutical company or healthcare lobbying group.
- I am Pharma-Free – not even any pens.

Thyroid Controversies

- Testing – TSH +/- FT4.
- T3 supplementation.
 - Whole thyroid preparations.
 - Adding T3 to levothyroxine.
- Management of subclinical thyroid dz.
- Screening for thyroid dz.
- Thyroid CA.
- Coconut oil.

Thyroid Controversies: Today

1. Testing – TSH +/- FT4.
2. T3 supplementation.
 - a) Whole thyroid preparations.
 - b) Adding T3 to levothyroxine.
3. Management of subclinical thyroid dz.
4. Screening for thyroid dz.

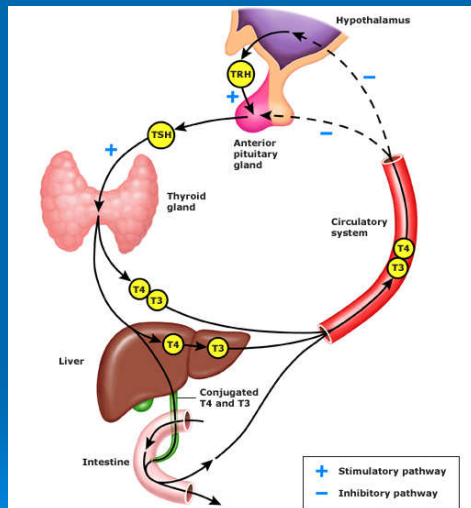
#1: Which Test(s) Should I Use?

- TSH
- T4
- FT4
- FT4I
- T3
- FT3
- T3RU

Review of Thyroid Hormones

- T4 = thyroxine:
 - 99.97% of T4 is **protein bound** (2 **ng**/dL = free).
 - Produced **exclusively by thyroid**.
 - Half-life ~ 1 week.
 - ~10 X **more prevalent** in serum than T3.
- T3 = triiodothyronine:
 - 99.7% of T3 is **protein bound** (0.4 **ng**/dL = free).
 - **80% comes from conversion** of T4 → T3 in peripheral tissues.
 - Half-life ~ 1 day.
 - 3-100 (~10) times **more potent** than T4.

<http://www.thyroidmanager.org/Chapter6a/6a-frame.htm>



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Total T4 & T3

- **Total T4 & Total T3 assays are rarely clinically useful in & of themselves, and should generally only be ordered in conjunction with an estimate of free (vs bound) hormone.**
 - Some experts note that total T3 is about as accurate as FT3 with current assays. Controversial.
 - Same is **NOT** true for T4—FT4 is preferred.

Free Hormone Hypothesis

- Free hormone hypothesis: **only free hormone is available to be active in the body**, whereas hormone bound to proteins (TBG, transthyretin, albumin) is inactive.

<http://www.thyroidmanager.org/Chapter6a/6a-frame.htm>

Measuring Free Thyroid Hormones

- So: we are trying to measure fractions of ng/ml quantities.
- Note: **there is NO measurement method that is truly accurate at measuring free thyroid hormones.**
 - “Index” tests (stay tuned) & immunoassays are protein-dependent & inaccurate if binding proteins abnormal.
 - Reference methods have technical problems & are expensive.

<http://www.thyroidmanager.org/Chapter6a/6a-frame.htm>

Free Thyroxine Index

- In the days before RIA & EIA & ELISA, we had to estimate free T4 (FTI/FT4I—less accurate).
- Today, the Free Thyroxine Index (FTI, FT4I, “T7”) is rarely used. We have better measurements for free T4.
- T3RU is NOT a measure of ANY thyroid hormone—it is ONLY to estimate free hormone.

Free Thyroid Hormone Tests

- **TSH is the single best thyroid test.**
- In most clinical situations involving **discordant** FT4 and TSH results, the **TSH usually** provides the most reliable results.
 - Tune in later for exceptions.
- **For most ambulatory patients, your lab's Free T4 & Free T3 assays (usually EIA or related assay) are good enough.**
- **Avoid Free Thyroxine Index whenever possible.**

<http://www.thyroidmanager.org/Chapter6a/6a-frame.htm>

Demystifying Thyroid Testing

- 1st test is high sensitivity or 3rd generation TSH (detection limit = 0.01).
- Normal TSH has a high negative predictive value (i.e., if WNL, likely rules out thyroid dz).

Thyroid 2003;13:57-67; <http://www.thyroidmanager.org/chapter/assay-of-thyroid-hormones-and-related-substances/>; <http://www.thyroidmanager.org/chapter/clinical-strategies-in-the-testing-of-thyroid-function/>

Interpretation of TSH

- High TSH → hypothyroid
 - Pituitary thinks there's insufficient thyroid hormones, so it secretes more TSH.
- Low TSH → hyperthyroid
 - Pituitary thinks there is plenty of thyroid hormones, so it shuts down TSH production.
- There are rare exceptions.

Thyroid "Set Point"

- Each person has low variability in TSH.
 - 0.5 month-to-month variability.
 - Variation in an individual is ~ ½ the variation of the population reference range.
 - TSH chg 0.2 – 1.6 could → chg in thyroid status.
 - ~2/3 of TSH "set point" is genetically determined.
- Result in "normal range" may not be normal for that person.
 - Tricky. (Watch for change over time.)

ClinChemLabMed 2005;43:102-5;JCEM 2002; 87:1068-1072; Clin Endocrinol 2008; 68:652-659; JCEM 2004; 89:1181-1187; JCEM 1988;66:588-92; EurJEndo 2011;164:781-8

FT4 Monitoring

- Note: FT4 is not sensitive for monitoring LT4 therapy.
- Exceptions, whereby FT4 testing may be useful:
 - Early in treatment for hypothyroidism (use w/TSH).
 - Pituitary deficiency (stop ordering TSH).

ClinEndo(Oxf) 1988;28:325-33

What is the “Normal Range” of TSH?

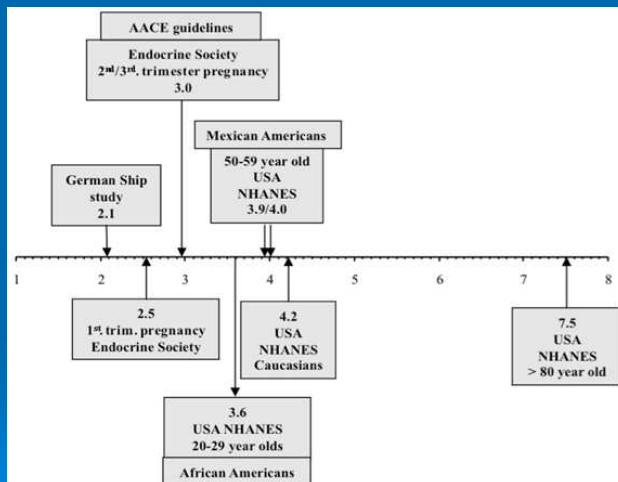
- Lower limit of range for 3rd generation tests is 0.3 – 0.4, regardless of population

JCEM 1988;66:588-92; NHANES III--JCEM 2002;87:489-99; ClinChemLabMed 2005;43:102-5

What is the Upper Limit of Normal for TSH?

- Quest Lab: 4.50
- Sutter Lab: 5.40
- National Academy of Clinical Biochemistry: 2.5
 - Based on rigorously screened euthyroid volunteers.
- Endocrine Society: 2.5
- > age 80: 7.49

Thyroid 2003;13:57-67; JCEM 2007;92:S1-47; JCEM 2007;92:4575-4582



<http://www.thyroidmanager.org/Chapter6a/6a-frame.htm>

TSH Upper Limit of Normal

- Most young – middle-aged euthyroid people have a TSH below 2.5 – 3.6.
- A TSH of 5 is likely above normal for a **young, healthy** person.

ClinChem 2005 Aug;51(8):1480-6

TSH Upper Limit of Normal – 2

- Reducing the upper limit of TSH range to 2.5 will likely label a sizable number of people as “abnormal” (or subclinical hypothyroidism).
 - Reducing ULN to 3.0 → 20% of Americans characterized as biochemically hypothyroid.
 - “...might significantly increase the use of thyroxine therapy for patients in whom there is no demonstrated therapeutic benefit.”

JAMA 2003;290:3195-6

When is TSH Less Accurate?

- Abnormal pituitary function (TSH is rarely undetectable in hypopit, except post-destruction or surgery).
- Non-thyroidal illness (“sick euthyroid”).
 - Includes hospitalized pts.
 - TSH still usually most reliable thyroid test.

BestPrac Res ClinEndocrinolMetab 2009;23:793–800; Lancet 2001; 357:1013-4; JCEM 1983;57:380-3; WJM 2000;172:102-6; <http://bestpractice.bmj.com/best-practice/monograph/1121.html>; http://www.cks.nhs.uk/hypothyroidism/management/scenario_diagnosis/interpreting_the_results/misleading_tsh_results; <http://www.endotext.org/neuroendo/neuroendo12/neuroendoframe12.htm>

When is TSH Less Accurate? – 2

- Renal failure (↑ TSH).
- Recovery from thyroiditis.
- 1st 3-4 months of treatment of hyper- or hypothyroidism.
- Starvation, caloric deprivation (?).
- Drugs affecting TSH.

BestPrac Res ClinEndocrinolMetab 2009;23:793–800; Lancet 2001; 357:1013-4; JCEM 1983;57:380-3; WJM 2000;172:102-6; <http://bestpractice.bmj.com/best-practice/monograph/1121.html>; http://www.cks.nhs.uk/hypothyroidism/management/scenario_diagnosis/interpreting_the_results/misleading_tsh_results; <http://www.endotext.org/neuroendo/neuroendo12/neuroendoframe12.htm>

Drugs That Affect TSH

- Falsely ↓ TSH:
 - **Glucocorticoids** (≥ 20 mg/day prednisone).
 - **Dopamine**, bromocriptine, levodopa.
 - Dopamine agonists alone do not cause significant central hypothyroidism – can in combo w/non-thyroidal illness (“sick euthyroid syndrome”).
 - Somatostatin analogs (octreotide).
 - Metformin?

BestPrac Res ClinEndocrinolMetab 2009;23:793–800; Lancet 2001; 357:1013-4; JCEM 1983;57:380-3; WJM 2000;172:102-6; DiabetesCare2009;32:1589-90; ClinEndo(Oxf) 2012; 2012 Jun 12. doi: 10.1111/j.1365-2265.2012.04468.epub; <http://www.thyroidmanager.org/chapter/assay-of-thyroid-hormones-and-related-substances/>

Drugs That Affect TSH – 2

- Falsely ↑ TSH (usu <10):
 - Dopamine antagonists (neuroleptics, metoclopramide).
 - Amphetamine
 - Theophylline
 - Iodinated contrast

BestPrac Res ClinEndocrinolMetab 2009;23:793–800; Lancet 2001; 357:1013-4; JCEM 1983;57:380-3; WJM 2000;172:102-6; DiabetesCare2009;32:1589-90; <http://www.thyroidmanager.org/chapter/assay-of-thyroid-hormones-and-related-substances/>

Drugs That Affect Free T4

- Falsely ↓ FT4:
 - Androgens (anabolic steroids)
 - Niacin
 - Phenytoin
 - Carbamazepine
 - Phenobarbital

EndocrinolMetabClinNAmer 2001;30:265-89; BestPracResClinEndoMetab 2009;23:753-67; PedEndoRev 2003;1:251-6; ClinChem 2000;46:1395-1400; WJM 2000;172:102-6; www.thyroidmanager.com

Drugs That Affect Free T4 – 2

- Falsely ↑ FT4:

<ul style="list-style-type: none"> • Estrogen • Heroin • Methadone • Amiodarone • Heparin, esp IV • Phenytoin 	<ul style="list-style-type: none"> • High-dose salicylates • Furosemide (IV >80 mg/day) • Propranolol, β-blockers • Iodinated contrast
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EndocrinolMetabClinNAmer 2001;30:265-89; BestPracResClinEndoMetab 2009;23:753-67; PedEndoRev 2003;1:251-6; ClinChem 2000;46:1395-1400; QJM 2001;94:471-3; WJM 2000;172:102-6; ClinEndo(Oxf) 1987;26:423-31; JCEM 1987;65:1259-64; www.thyroidmanager.com

Drugs That Affect Thyroid Function

- Combo:
 - Amiodarone (hypo, hyper, mult mechs).
 - Interferon (Hep C, MS).
 - 5% hypo, 3% hyper, 2% biphasic.
 - 1/3 persist after treatment.
 - Lithium (usu hypo, may be assoc w/hyper).
 - Iodine, radiocontrast.
- Hypo:
 - Retinoids, vitamin A (high dose)

WJM 2000;172:102-6; AmJMed 1993;95:78-82; www.thyroidmanager.com

Secondary Hypothyroidism

- Low TSH & low (or low-normal) Free T4
 - May have normal or slightly high TSH – **inappropriate** for low level of FT4 (tricky—FT4 reliability).
 - 84% normal TSH.
 - 8 – 25% mildly elevated (5-10).
 - Normal TSH in these pts may be due to TSH w/↓ biologic activity but normal immunoreactivity to test.

Pituitary 2008;11:181-6; EurJEndocrinol 2004 Jan;150:1-8; JCEM 2000;85:3631-5; EndocrinolMetabClinNorthAm 2000;29:399-415; <http://www.uptodate.com/content/central-hypothyroidism>

Low(-ish) FT4 + SI High TSH

- Get anti-TPO
 - If + → autoimmune thyroiditis (Hashimoto's) → 1°.
- Get pituitary hormones (FSH, LH) +/- E2 or T.
 - Low FSH/LH, esp in postmenopausal woman, → pituitary dz.
 - Low T + low or NI LH in men → pituitary.
 - Prolactin not reliable – can be ↑ in either.

<http://www.uptodate.com/contents/central-hypothyroidism>

Secondary Hypothyroidism – 2

- Rare – ≤1% of hypothyroidism.
- Causes:
 - Brain lesion (tumor, cyst, abscess).
 - Pituitary hemorrhage or infarction.
 - Iatrogenic – surgery, radiation.
 - Infiltrative – sarcoidosis, TB, other.

Pituitary 2008;11:181-6; EurJEndocrinol 2004 Jan;150:1-8; JCEM 2000;85:3631-5; <http://www.uptodate.com/content/central-hypothyroidism>

When to Suspect 2° Hypothyroidism

- Known hypothalamic or pituitary disease.
 - Traumatic brain injury.
 - Sheehan's syndrome.
 - SAH.
 - Prior surgery or radiation.
 - Young woman w/amenorrhea.
- Mass lesion in the pituitary.
- Symptoms and signs of hypothyroidism are associated with other hormonal deficiencies.

2° Hypothyroidism

- 26 cases of hypopituitarism/56,000 tests & population of 471,000 → 0.00047% of tests & 0.000055% of population.
- BUT missed hypopit is problematic.
 - Litigation.
 - Missed dz, morbidity, burden of suffering.
- Big expense to **routinely** do both tests.
- Is it worth it to abandon “TSH-first” strategy, and get TSH + FT4 on all? Probably not at present. Stay tuned....

Lancet 2001;357:1013-4; ClinEndocrinol 2003;56: 20-1

What Time of Day to Test TSH?

- Diurnal variation, peak 00:00 – 04:00.
- However, in ambulatory pts, TSH is tested during daytime hrs and results are not/less affected by time of day.
- Do NOT need to hold LT4 to test TSH.
 - TSH secretion responds slowly to changes in T4 status.
 - This is why you wait 6-8 weeks to recheck TSH after med change.

JCEM 1991;72:145-150; Thyroid 2003;13:57-67

Ambulatory vs Hospital

- In ambulatory pts, TSH is generally the best test.
 - Some suggest low threshold for checking free T4 (i.e., still TSH-first).
- In hospital: thyroid hormone tests are all acutely +/- chronically affected by illness.
 - **Thyroid testing should be avoided in acutely ill pts, except when the patient's history or clinical features suggest thyroid dysfunction, esp as the main cause of the current problem.**

Lancet 2001;357:1013-4; ClinicalThyroidology 2001;13:35; <http://www.nacb.org/>; EndocrinolMetabClin NAm 2001;30: 265-89; Clin Chem 1996; 42:188-92

TSH: The Future (We Hope)

- TSH normal values may be age-related.
 - Normal values in children ≠ adult normals.
- Other factors that may affect TSH:
 - Gender (F>M)
 - Ethnicity (Caucasians>Latinos>African-Americans)
 - Smoking (lowers TSH & may be assoc'd w/less hypothyroidism)

ClinEndocrinol 2009;70:788-793; JCEM 2010;95:496-502; JCEM 2002;87:489-499

When Should I Order FT3?

- Known or suspected **hyperthyroidism**.
- Early in course of treatment for **hyperthyroidism**.
 - TSH may remain suppressed for weeks – months early in tx.
- Maybe in pts receiving whole thyroid preps (Armour, Thyrolar)—avoid **hyperthyroidism**.
 - Mostly anecdotal, not great evidence.
- Dx of amiodarone-induced **hyperthyroidism**.

www.thyroidmanager.org/chapter/clinical-strategies-in-the-testing-of-thyroid-function/

Thyroid Autoantibodies

- Anti-thyroglobulin (anti-Tg).
 - 5-20% of general population.
- Anti-thyroid peroxidase (anti-TPO).
 - 8-27% of general population.

<http://www.utdol.com/online/content/image.do?imageKey=ENDO%2F5488;>
http://www.utdol.com/online/content/topic.do?topicKey=thyroid/7938&selectedTitle=2%7E150&source=search_result

Thyroid Autoantibodies – 2

- Hashimoto's:
 - TPO: 90% +
 - Tg: 80-90% +
- Graves':
 - TPO: 50-90% +
 - Tg: 50-70% +
- DM1: 30-40% + for each.
- Relatives of Hashimoto's: 30-50% + for each.

[http://www.utdol.com/online/content/topic.do?topicKey=thyroid/7938&selectedTitle=2%7E150&source=search_result;](http://www.utdol.com/online/content/topic.do?topicKey=thyroid/7938&selectedTitle=2%7E150&source=search_result) <http://www.utdol.com/online/content/image.do?imageKey=ENDO%2F5488>

Why Get Antithyroid Ab's?

- Generally unnecessary.
 - If **hypothyroid**, 90+% Hashimoto's.
 - Most of the rest are thyroiditis or iatrogenic.
 - 2° will still get same treatment.
- May provide prognostic info in pts @ high risk:
 - Such as pregnant women w/thyroid dysfunction – may **predict** later Graves'.
 - May help in dx & prediction of **subclinical** thyroid dz.

General Rule of Thyroid Tests

Do not interpret thyroid test results in a vacuum – you must look at the clinical picture!

#2: What About T3 Therapy?



Stop the thyroid madness™! It's not working. It never has! It still doesn't.
P.S. Still think this site may not apply to you? Go [here](#) for more information.

If only meds
don't work

TSH - Why
It's Useless

Hypothyroid
Symptoms

Stories of
Others

<http://www.stopthethyroidmadness.com/>

- > Less stamina than others
- > Less energy than others
- > Long recovery period after any activity
- > Inability to hold children for very long
- > Always feeling like dead weight after activity
- > Chronic Low Grade Depression
- > Suicidal Thoughts
- > Often feeling cold
- > Cold hands and feet
- > High or rising cholesterol
- > Heart disease
- > Palpitations
- > Fatigations
- > Plaque buildup
- > **Bizarre and Debilitating reaction to exercise**
- > Hard stools
- > Constipation
- > No eyebrows or thinning outer eyebrows
- > Dry Hair
- > Hair Loss
- > White hairs growing in
- > No hair growth, breaks faster than it grows
- > Dry cracking skin
- > Numbness of easily
- > Requires naps in the afternoon
- > Sleep Apnea (which can also be associated with low cortisol)
- > Air Hunger (feeling like you can't get enough air)
- > Inability to concentrate or read long periods of time
- > Forgetfulness
- > Foggy thinking
- > Inability to lose weight
- > Always gaining weight
- > Inability to function in a relationship with anyone
- > **NO sex drive**
- > Failure to ovulate and/or constant bleeding (see Rainbow's story)
- > Moody periods
- > PMS
- > Inability to get pregnant; miscarriages
- > Excruciating pain during period
- > Nausea
- > Swelling/edema/puffiness
- > Aching bones/muscles
- > Osteoporosis
- > Bumps on legs
- > Acne on face and in hair
- > Breakout on chest and arms
- > Hives
- > Exhaustion in every dimension—physical, mental, spiritual, emotional
- > Inability to work full time
- > Inability to stand on feet for long periods
- > Complete lack of motivation
- > Slowing to a snail's pace when walking up slight grade
- > Extremely crabby, irritable, intolerant of others
- > Handwriting nearly illegible
- > Internal itching of ears
- > Broken/peeling fingernails
- > Dry skin or snake skin
- > Major anxiety/worry
- > Ringing in ears
- > Lactose intolerance
- > Inability to eat in the mornings
- > Joint pain
- > Carpal tunnel symptoms
- > No Appetite
- > Fluid retention to the point of Congestive Heart Failure
- > Swollen legs that prevented walking
- > Blood Pressure problems
- > Varicose Veins
- > Dizziness from fluid on the inner ear
- > Low body temperature
- > Poised temperature
- > Tightness in throat; sore throat
- > Swollen lymph glands
- > Allergies (which can also be a result of low cortisol—common with hypothyroid patients)
- > Headaches and Migraines
- > Sore feet (plantar fasciitis); painful soles of feet
- > now how do I put this one politely...a cold bum, butt, derriere, fanny, gluteus maximus, haunches, hindquarters, posterior, rear, and/or cheeks. Yup, really ewww.
- > colitis
- > irritable bowel syndrome
- > painful bladder
- > Extreme hunger, especially at nighttime
- > Dysphagia, which is nerve damage and causes the inability to swallow fluid, food or your own saliva and leads to "aspiration pneumonia".

Why Consider Adding T3?

➤ Some hypothyroid pts still feel poorly on LT4.

- Neurocognitive testing → still poor performance on tests of memory (esp immediate), attention, overall well-being.
- 2nd study: impaired psychological well being in hypothyroid pts on LT4.

BMJ 1970;2:270-1; ClinEndoMetab 1979;8:39-48; EurJEndo 2005;153:747-53; ClinEndo(Oxf) 2002;57:577-85

Does T3 Help?

- Converting 50 mcg of total LT4 dose to 12.5 mcg of LT3 (placebo-controlled):
 - No change in TSH.
 - FT4 decreased.
 - T3 increased.
 - Testing → improved fatigue, depression, global mood.
 - Visual-analog scale → improved mood, some sx (cold intol, blurred vision, nausea).
 - Most had been Tx'd for thyroid CA.

NEJM 1999;340:424-9

Evidence: T3 Doesn't Help

- Neurocognitive function & psych well-being may not return to normal w/LT4.
- **The vast majority of studies show no advantage to T3 supplementation or partial replacement (10/12 + meta-analysis).**
- Risk of hyperthyroidism & long-term effects.

EurJEndol 2005;153(6):747-53; ClinEndo(Oxf) 2002;57(5):577-85; NEJM 1999;340(6):424-9; JCEM 2003;88(10):4543-50; JCEM 2003;88(10):4551-5; JAMA 2003;290:2952-8; ClinEndocrinol(Oxf) 2004;60:750-7; AnnIntMed 2005;142:412-24; JCEM 2005;90:805-12; JCEM 2005;90:2666-74; EndocrPract 2005;11:223-33; JCEM 2005;90:4946-54; JCEM 2006;91(7):2592-9; JCEM 2003;88:4540-2; http://www.utdol.com/online/content/topic.do?topicKey=thyroid/2117&selectedTitle=3%7E150&source=search_result#H13

More Recent Study

- Adjusted T3 dose (not fixed-dose combo):
 - TSH levels similar in both groups (T4 vs T4+T3).
 - Limited to pts w/autoimmune thyroiditis.
 - Results:
 - QOL improved – 7/11 measures.
 - 49% preferred combo Rx.
 - 15% preferred T4 only.
- Pts tend to prefer T4+T3 combo to T4 alone.

EurJEndo 2009;161:895-902; EurJEndo 2009;161:955-9; JCEM 2005;90:2666-74; NEJM 1999;340(6):424-9

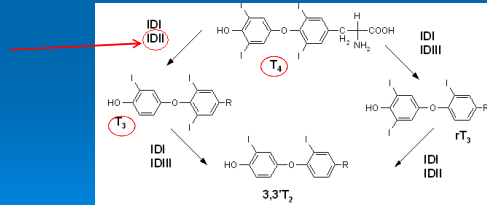
An Opposing Study

- 697 hypothyroid pts:
- Validated instruments to assess psych well-being.
 - FT4 & TSH had strong correlation with psych well-being.
 - No correlation to psych well-being:
 - FT3
 - rT3, rT3:FT4, FT3:rT3

JCEM 2006;91:3389-93

Caveat and Interesting Info

- There may be a **subgroup who respond to T3** (deiodinase gene polymorphism).
 - Up to 16% may have a deiodinase gene polymorphism. Some of these pts may feel better w/**appropriate** T3 supplementation.



JCEM 2009;94:1623-9; AmJPhysiol 1990;258:E715-26; Thyroid 2004;14:271-5; ClinEndo 2009;70:954-60; JCEM 2008;93:3075-80

How Much T3?

- Physiologic T4:T3 ratio in humans is ~ 10-14:1.
 - Armour Thyroid & Thyrolar have 4:1 of T4:T3.
 - Both have high T3 for humans.
 - Amount of Armour to maintain normal TSH produces FT4 in lower normal range, & variable T3.
 - Amount to help pt feel better generally lowers TSH below normal – hyperthyroid range.
 - FDA recall in 2005 – **inconsistent/unstable** levels.
 - FDA recall 2011 for mislabeling. Armour no longer licensed in UK.

www.thyroidmanager.org/chapter/adult-hypothyroidism; www.fda.gov

How Much T3? – 2

- **Trial of ~10:1 ratio of T4:T3 may be reasonable.**
- T3 (Cytomel™) best taken bid (or slow release – unavailable in US).
 - 2nd dose midday or afternoon.
 - Comes in 5, 25, 50 mcg.

How Do You Do It?

- **Reduce LT4** dose by the amount of added T3.
 - Pt on 125 mcg LT4.
 - 1/10 of dose = 12.5 mg.
 - Options:
 - ½ of 25 mcg pill = 12.5 mcg, split into am & pm doses + give LT4 112 mcg.
 - 5 mcg T3 bid + 112 +/- ¼ of 25 (=6.25).

Monitoring T4 + T3 Therapy

- Avoid overtreating to hyperthyroidism.
MONITOR!
- Monitor TSH, esp when using LT4 + T3.
- Insufficient evidence regarding desiccated thyroid monitoring.
 - TSH may stay suppressed long term.
 - FT4 + probably FT3.
- Adjust T4 &/or T3 doses as appropriate.

Monitoring of LT4 Treatment

- **Goal = TSH of 0.5 – 2.0.**
 - Measure TSH q 6 weeks. **TSH takes 6 weeks to equilibrate** after change in thyroid meds (or change in endogenous function).
- If monitoring FT4 &/or FT3 (i.e., combo therapy), goal is usually upper ½ of normal range.

HormRes 2001;56(Suppl1):74-81; www.thyroidmanager.org/chapter/adult-hypothyroidism/#toc-9-8-treatment-of-hypothyroidism

Exogenous Subclinical Hyperthyroidism Risks

- Osteoporosis:
 - Uncertain.
 - Loss of BMD probably occurs in postmenopausal women w/suppressed TSH on meds; probably not (or small effect) in premenopausal women.
 - Fx risk may or may not be increased (men & women).

EurJEndocrinol 1994;130:350-6; JCEM 1996;81:4278-89; JCEM 1994;78:818-23; ClinEndo(Oxf) 1994;41:747-55; AnnIM 2001;134:561-8; JCEM 2010;95:186-93; ClinEndo(Oxf) 1992;37:500-3; ArchIM 2010;170:1876-83; ClinEndo 1997;47:529-35

Exogenous Subclinical Hyperthyroidism Risks – 2

- Atrial fibrillation:
 - ↑ risk w/exogenous (meds) or endogenous hyperthyroidism, esp in elderly.
 - RR ~ 2-3 for TSH <0.1; ~ 0-1.6 for TSH 0.1-0.4.
- Palpitations, supraventricular arrhythmias.
- LVH/↑ LV mass (major CV risk factor).
- ↓ diastolic function.
- ??CAD

NEJM 1994;331:1249-52; JCEM 1994;78:1028-33; JCEM 1997;82:2592-5; JCEM 2000;85:159-64; JCEM 1993;77:334-8; Cardiologia 1999;44:443-9; EurJEndo 2005;152:1-9; BMJ 1984;289:1645-7; ArchIM 1989;149:809-12; Heart 1996;75:363-8; JCEM 1995;80:2222-6; ClinEndo(Oxf) 1992;37:500-3

Desiccated Thyroid → LT4

- 1 grain (60 mg) of Armour Thyroid contains ~74 mcg of LT4 equivalent.
 - Armour has high T3 content.
 - If changing TO LT4 FROM Armour, some recommend assuming 60 mg of Armour ~ 100 mcg of LT4 (lose T3 “buzz”—rapid action).
- Variable T3 & other factors can lead to prolonged ↓ TSH, even after stopping Armour.

www.uptodate.com/contents/treatment-of-hypothyroidism; www.thyroidmanager.org/chapter/adult-hypothyroidism

#3: Subclinical Thyroid D/O's

- Definitions (not truly “subclinical”):
 - Subclinical hypothyroidism = ↑ TSH + normal FT4.
 - Subclinical hyperthyroidism = ↓ TSH + normal FT4 & FT3.
- Where is the “clinical”?
 - Sx absent or mild.
- TSH usually <10, & without sx.

EndocrRev 2008;29(1):76-131; Lancet 2012;379:1142-54

Subclinical Hypothyroidism

- Common
 - NHANES III: prevalence = 4.3% (93% of all hypothyroidism detected was subclinical!).
 - Other studies: prevalence = 3 – 15%.
- More common in Caucasians & women, & probably > age 75.
- May be more prevalent in iodine-sufficient areas.

JCEM 2002;87:489-99; JFamPrac 1994;38:583-8; ArchIM 1990;150:785-7; ArchIM 2002;162:773-9; ArchIM 2000;160:526-34; ClinEndo(Oxf) 1997;47:87-92

Diagnosis

- Repeat TSH + FT4 in at least 4-6 weeks, except when treatment is indicated:
 - Pregnancy—no time to wait!
 - Infertility

Not Subclinical Hypothyroidism

- After non-thyroidal illness (“sick euthyroid”).
- Post-thyroiditis (transient hypo).
- Untreated adrenal insufficiency.
- Drugs (see above).
- Central hypothyroidism (see above).

EndocrReview 2008;29:76–131

Complications of Subclinical Hypothyroidism

- Progression to true hypothyroidism: 33 – 55%.
 - May be more likely if TSH >10.
 - RR = 8 for women; RR = 44 for men.
 - ↑ risk if + anti-TPO (prognostic factor).
 - RR = 8 for women; RR = 25 for men.
 - Both:
 - RR = 38 for women; RR = 173 for men.

JCEM 2002;87:3221-6; ClinEndo(Oxf) 1995;43:55-68; ArchIM 1993;153:957-61; JCEM 2005;90:4124-7

Complications of Subclinical Hypothyroidism – 2

- Cardiovascular – uncertain.
 - CAD risk – maybe only if TSH >10.
 - CHF risk – maybe only if TSH >10.
 - Diastolic dysfunction – maybe only if TSH >10.
 - ? ↑ CV &/or all-cause mortality if TSH >10.

JAMA 2010;304:1365-7; AnnIM 2000;132:270-8; Thyroid 2003;13:595-600; JCEM 2004;89:3365-70; ArchIM 2005;165:2467-72; JCEM 2010;95:1734-40; ArchIM 2005;165:2460-6; JAMA 2006;295:1033-41; Circulation 2012;126:1040-9; JCEM 1999;84:2064-7; JCEM 2007;92:3504-10; Thyroid 2011;21:837-43; JACC 2012;60:730-7; JCEM 2012;97:862-70; ArchIM 2000;132:270-8

Complications of Subclinical Hypothyroidism – 3

- Weight gain.
- Non-alcoholic fatty liver dz.
- Poss ↑ risk of Alzheimer dz in women only.

ArchIM 2008;168:587-92; JCEM 2005;90:4019-24; JHepatol 2012;57:150-6; ArchIM 2008;168:1514-20

Complications of Subclinical Hypothyroidism – 4

- Poor pregnancy outcomes:
 - Severe **pre-eclampsia**.
 - Preterm delivery.
 - Pregnancy loss.
 - Placental **abruption** (!!?) – RR = 3.
 - ? Cognitive impairment – ↓ IQ at age 7-9, even w/o overt hypothyroidism of child.
 - 64% of untreated preg women developed overt hypothyroid, vs 4% of matched controls.

Thyroid 2005;15:351-7; ObstetGynecol 2005;105:239-45; ObstetGynecol 2012;119(2 Pt 1):315-20; NEJM 1999;341:549-55; NEJM 2012;366:493-501

Does Treatment Help?

- Symptoms: maybe, esp if TSH > 10.
- Cardiovascular: limited data.
 - Risk factors improve—lipids, diastolic dysfx.
 - Limited outcomes data (published May 2012):
 - Ages 40 – 70: 39% ↓ in ischemic events.
 - > age 70: no difference.
- Pregnancy: probably beneficial.

JGenIM 1996;11:744-9; JCEM 2001;86:4860-6; CochraneRev 2007 Jul 18;(3):CD003419; JCEM 2007;92:1715-23; JCEM 2006;91:145-53; AmJMed 2002;112:348-54; ArchIM 2012;172:811-817; <http://www.uptodate.com/contents/subclinical-hypothyroidism>

Consider For Treatment

- Probably TSH > 10.
- TSH <10:
 - Symptomatic – trial of LT4.
 - High CV risk – DM, diastolic dysfx, smoker,....
 - Pregnancy, or pre-conception counseling.
 - Asymptomatic – can monitor TSH, Rx prn.
 - No good evidence to Rx > age 70, poss harm (overtreatment to overt/subclin hyper → CV risk).

EndocrRev 29:76–131; JCEM 2009;94:1342-5; <http://www.uptodate.com/contents/subclinical-hypothyroidism>

Subclinical Hyperthyroidism

- Less common.
 - 0.7% prevalence, > ½ asymptomatic.
- More common in women, smokers, elderly.
- 40-76% return to normal TSH within 1 yr.

JCEM 2002;87:489-99; JCEM 2004;89:6077-86; ClinEndo(Oxf) 1991;34:77-83; ArchIM 2007;167:1533-8

Subclinical Hyperthyroidism – 2

➤ Causes:

- Meds (“exogenous”).
- Endogenous:
 - Autonomously functioning (“hot”) nodule.
 - Multinodular goiter.
 - Thyroiditis.

Thyroid 1996;6:391-6; <http://www.uptodate.com/contents/subclinical-hyperthyroidism>

Risks of Subclin Hyperthyroidism

➤ Progression to overt hyperthyroidism.

- Depends on cause: hot nodule > nodular goiter > Graves’.
- More likely to progress in 1st year, tends to be more stable after that.
- More likely to progress if TSH <0.1.
- Uncommon in elderly w/subclin hyperthyroidism (1-4%).

ClinEndo(Oxf) 2011;74:257-61; JCEM 2011;96:1344-51; ClinEndo(Oxf) 2008;68:491-2; ClinEndo(Oxf) 2012;77:146-51; ClinEndo(Oxf) 2010;72:685-8; ArchIM 1991;151:165-8

Risks of Subclin Hyperthyroidism – 2

- Osteoporosis – esp postmenopausal.
- Hip fx.
- Mortality – uncertain (all-cause, CV).
 - ↑ risk w/TSH <0.1.
 - Risk may ↑ w/age.
- **Subclinical hyperthyroidism** in pregnancy was **NOT** assoc’d w/adverse outcomes.

Thyroid 1994;4:319-26; AnnIM 1994;120:8-11; ClinEndo(Oxf) 1995;43:339-45; NEJM 1995;332:767-73; JIntMed 1995;237:241-7; ArchIM 2012;172:799-809; JCEM 2010 ;95:186-93; ObstetGynecol 2006;107(2 Pt 1):337-41

Subclinical Thyroid Dz in Pregnancy

In pregnancy: It is better to be slightly hyper- than slightly hypo-thyroid.

Risks of Subclin Hyperthyroidism – 3

- Cardiovascular:
 - Atrial fibrillation – esp if TSH<0.1.
 - CAD/ischemic events.
 - CHF (HR 2-3), esp TSH <0.1.
 - LVH.
- ? ↓ **Quality of life**?!?

ArchIM 2012;172:799-809; NEJM 1994;331:1249-52; JCEM 2011;96:1344-51; JCEM 2012;97:852-61; Circulation 2012;126:1040-9; EndocrRev 2008;29:76-131

NOT Subclin Hyperthyroidism

- ↓ TSH + normal FT4 & FT3:
 - Central hypothyroidism—T4/T3 may be nl-low.
 - Non-thyroidal illness – incl glucocorticoids.
 - Recovery from hyperthyroidism.
 - TSH may remain ↓ for up to several months p-normalization of T4 & T3 in pts treated for hyperthyroidism or recovering from hyperthyroidism caused by thyroiditis.
- Dx aid: radioiodine uptake & scan.
 - ↑ uptake or hot nodule → subclin hyper.

<http://www.uptodate.com/contents/subclinical-hyperthyroidism>

Is Treatment Beneficial?

- Data are sparse.
 - Treatment with antithyroid drugs or radioiodine ablation slows bone loss.
 - For treatment of differentiated thyroid CA, benefits of treating to subclinical hyperthyroidism are believed to outweigh risks.
- Repeat TSH, consider treating only if it stays low.

ClinEndo(Oxf) 1991;34:77-83; ClinEndo(Oxf) 1994;41:421-4; ClinEndo(Oxf) 1998;48:285-9; <http://www.uptodate.com/contents/overview-of-the-management-of-differentiated-thyroid-cancer>

Risk-Based Tx Approach

- High risk for complications (elderly, arrhythmia risk, osteoporosis risk, etc):
 - TSH < 0.1 → treat.
 - TSH 0.1-0.4 → treat if underlying CV dz or low BMD.
 - Treat hot nodules – more likely to progress.
- If obs & not tx, follow TSH + FT4 + FT3 q 6 mo.

JAMA 2004;291:228-38; EndocrRev 2008;29:76-131; <http://www.uptodate.com/contents/subclinical-hyperthyroidism>

Risk-Based Tx Approach – 2

- Low risk for complications (young, premenopausal women):
 - TSH <0.1 mU/mL → treat underlying cause of subclinical hyperthyroidism if sx &/or if thyroid radionuclide scan shows hot nodule(s).
 - TSH 0.1 – 0.4 → observation (TSH, free T4, FT3 q6 mo).

JAMA 2004;291:228-38; EndocrRev 2008;29:76-131; <http://www.uptodate.com/contents/subclinical-hyperthyroidism>

#4: Screening for Thyroid D/O's

- American Thyroid Association (ATA) recommends screening every 5 years beginning at 35.
- USPSTF, AAFP: “evidence is insufficient to recommend for or against routine screening for thyroid disease in [nonpregnant] adults.”

<http://www.ahrq.gov/clinic/uspstf/uspsthyr.htm>; AnnIntMed 2004;140:128-41; JAMA 2004;292:2591-9

What Does the Data Say?

- No proven outcome advantage to routine screening.
- No association w/cognitive function, depressive sx, disability in ADLs in an elderly population.

<http://www.ahrq.gov/clinic/uspstf/uspsthyr.htm>; AnnIntMed 2004;140:128-41; JAMA 2004;292:2591-9

What Does the Data Say? – 2

- Subclinical hypothyroidism (higher TSH):
 - Assoc'd w/slower decline in "instrumental" ADLs.
 - Assoc'd w/↓ all-cause/CV mortality, despite higher baseline cholesterol(!).
- Consider targeted screening – risk factors.
- Insufficient data to justify universal screening during pregnancy – no outcome advantage.

<http://www.ahrq.gov/clinic/uspstf/uspsthyr.htm>; AnnIntMed 2004;140:128-41; JAMA 2004;292:2591-9; JCEM 2010;95:1699-707; NEJM 2012;366:493-501

Risk Factors for Thyroid Dz

- Hyper-/hypo-
 - Female gender
 - Age, esp older women > 60 – 65
 - Pregnancy/postpartum (be on the lookout for sx)
 - Prior thyroid problems
 - FH
- Hyper-:
 - Smoking
 - Life stressors (!?)
- Hypo-:
 - Autoimmune
 - Turner's
 - Small at birth or in childhood
 - Neck/chest radiation
 - HIV

http://www.uptodate.com/contents/disorders-that-cause-hyperthyroidism?source=search_result&selectedTitle=1-150

Drugs That Interfere w/LT4

- Acid reducers (PPI, probably H2, sucralfate)
- Bile acid sequestrants (cholestyramine)
- Ca⁺⁺, Carbamazepine
- Dilantin, Depressants (sertraline, maybe other SSRI's)
- Estrogen derivatives
- Fe
- Check drug interactions when prescribing

(C) David M Schneider, MD

Take Home Points

- Testing – TSH is still best, some role for FT4.
- T3 supplementation – may be worth a therapeutic trial.
 - Adding T3 to levothyroxine.
- Management of subclinical thyroid dz—who might be good candidates.
- Screening for thyroid dz.—don't listen to thyroidologists!