Assessment and Treatment of Thyroid Dysfunction

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Assessment and Treatment of Hypothyroid Dysfunction
Objectives:

- Analyse underlying causes for the high incidence of hypothyroid dysfunction in the general population.
- Recognise thyroid dysfunction through clinical assessment and laboratory evaluation.
- Evaluate the controversy regarding TSH assessment and subclinical hypothyroid, and recognise how to use and interpret this test as part of a broader assessment of thyroid dysfunction.
- Evaluate other important laboratory evaluations to perform in a patient suspected of thyroid dysfunction.
- Evaluate important treatment considerations.
What do we know that causes the thyroid to go awry?
How do you recognise it clinically?
What do you test for?
How do you treat short of HRT?
Thyroid Disease by the Numbers

- **27 Million**: The number of Americans estimated to suffer from Thyroid Disease.
- **13 Million**: The number of Americans estimated to suffer from Thyroid Disease…but remain undiagnosed.
- **14 Million**: The number of Americans estimated affected by Hashimoto’s Thyroiditis
- **8 out of 10**: The number of patients with Thyroid Disease who are women.
- **25%**: The percent of American women estimated to develop permanent hypothyroidism.

American Association of Clinical Endocrinologists (AACE)
Colorado State Fair Study

- 25,862 people at the Colorado Fair
- 9.5% had TSH values >5.01 mU/L
- 2.2% percent had TSH <0.3 mU/L
- Only 60 percent of people taking thyroid medication had TSH levels in the normal range (>0.3 and <5.01 mU/L)

It is estimated that one out of every seven adults in the United States has a low functioning thyroid.

American Thyroid Association Website.  
“The thyroid is the ‘sentinel’ gland for the environment.”

Jeff Bland PhD
“Hypothyroidism can affect all organ systems. These manifestations are largely independent of the underlying disorder but are a function of the degree of hormone deficiency.”

What are the Effects of Suboptimal Thyroid Function?

- Fatigue (mental and physical)
- Weight gain
- Cardiovascular dysfunction
  - Dyslipidemias
  - Atherogenesis
- Glucose intolerance/insulin resistance
- Poor pregnancy outcomes

**FUNCTIONAL MEDICINE MATRIX**

**Retelling the Patient’s Story**

### Antecedents

### Triggering Events

### Mediators/Perpetuators

### Modifiable Personal Lifestyle Factors

- **Sleep & Relaxation**
- **Exercise & Movement**
- **Nutrition**
- **Stress**
- **Relationships**

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**Physiology and Function: Organizing the Patient’s Clinical Imbalances**

- **Assimilation**
  - Decreased digestion and absorption, generally slowing of the GI tract
- **Defense & Repair**
  - Low grade inflammation
- **Biotransformation & Elimination**
  - Decreased mitochondrial energy production
  - Sensitivity and susceptibility to toxins
- **Transport**
  - Decreased motility

**Structural Integrity**

**Mental**

**Emotional**

**Spiritual**

**Energy**

**Communication**

- Receptor dysfunction
- Glucose intolerance
- Insulin Resistance
- Decreased motility

**Muscle pain**
What do we know that causes the thyroid to go awry?
How do you recognise it clinically?
What do you test for?
How do you treat short of HRT?
Why is there so much thyroid dysfunction?

• Stress
• Inflammation
• Infection
• Dietary factors
  – Gluten
  – Goitrogens
  – Low-calorie diet
  – Nutritional insufficiencies
• Medications
• Toxins
Stress and Thyroid Function

Stress suppresses:
• Hypothalamic release of TRH
• Pituitary release of TSH
• Production of thyroid hormones from the gland itself

Thompson, FK. Is there a thyroid cortisol depression axis? Thyroid Science, 2(10):1,2007
Stress/Cortisol and Suppression of Thyroid Function

Increased urinary cortisol metabolites have been associated with reduction in peripheral thyroid hormone metabolism and symptoms of functional hypothyroidism.

Why is there so much thyroid dysfunction?

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  - Nutritional Insufficiencies
- Medications
- Toxins
Stress

CRH → STS → TRH → TSH → T3 → T4

ACTH

TNF IL-10

Inflammation

Cortisol → rT3
Inflammation and suppression of thyroid function in FM patients

...high levels of inflammatory cytokines, have been associated with depressed levels of the active thyroid hormone T3 in fibromyalgia patients, suggesting these cytokines may downregulate the activity of the HPT axis.

Infections, Graves’ and Hashimoto's

1023 patients → 359 patients with Graves & 664 with Hashimoto's

CONCLUSIONS:
The different month of birth seasonality in both GrH and HH points toward...a seasonal viral infection as the initial trigger in the perinatal period, the clinical disease resulting from further specific damage over time.

Bacterial Infection

Higher incidence of *Yersina enterocolitica* antibodies in Graves’ and Hashimoto’s patients then in controls.

Corapcioglu, D., et al. Thyroid 2002:12 613-617
Why is there so much thyroid dysfunction?

- Stress
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- Infection
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  - Gluten
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Diet: Gluten, Coeliac Disease, and Thyroid Function

Study of 241 untreated coeliac disease patients vs. 212 controls confirmed that patients with coeliac disease are at increased risk for developing thyroid disease with an overall threefold higher frequency than in controls (30% vs. 11%).

After 1 year on a gluten-free diet:

- Subclinical hypothyroidism normalized in 10 of 14 (71%) patients with non-autoimmune disease.
- In three of five (60%) patients with autoimmune thyroid disease (AIT), there was a shift to AIT with euthyroidism.
- In four of five subjects with no improvement in thyroid function, compliance with the diet was poor.

A More Recent Study

• Reviewed 14,021 individuals with coeliac disease
• Greater then 4 fold greater chance of developing hypothyroidism if patient had Coeliac Disease (CD)
• For children with CD, that risk increased to 6 fold

AIT and DM1 are the Most Commonly Associated Autoimmune Diseases in Celiac Patients

Genetic linkage

– Gluten sensitivity is associated with HLA-DQ-2, DR-3, B8 antigens.
– Hashimoto’s associated with DR-3, DR-5 antigens
– Coeliacs who are not DR-3 are often DR-5/DR-7 positive.

Be on the Lookout for Nutrient Deficiencies in Celiac Disease

- Iron
- Zinc
- Folic acid
- B12
- Calcium
- Selenium
- Vitamin A
- Vitamin D
- Vitamin E
- Vitamin K
Diet: Goitrogens, Soy, and Thyroid Function

Animal studies show suppression…But…

Diet:
Soy and Thyroid Function

• When initiating soy-formula feeding in infants with congenital hypothyroidism, the L-thyroxine dose should be increased because of significant reduction in intestinal absorption.

• Conversely, when soy feeding is discontinued, the L-thyroxine dose should be decreased.

Diet: Soy and Thyroid Function

- Case report of a 45-year-old woman who had hypothyroidism after a near-total thyroidectomy and radioactive iodine ablative therapy.
- Required unusually high oral doses of levothyroxine to achieve suppressive serum levels of free T4 and TSH.
- She had routinely been taking a "soy cocktail" protein supplement immediately after her levothyroxine.
- Separation of the intake of the soy protein cocktail from the levothyroxine resulted in attainment of suppressive serum levels of free T4 and TSH with use of lower doses of levothyroxine.

Human Studies: Soy and Thyroid Function

• “Authors suggested were so minor as to not be of physiologic importance.”
• “Intragroup differences were statistically indistinguishable at 6 months.”
• “Authors concluded that the changes were of such a small magnitude that they were unlikely to be clinically important.”

Recent Review

- 14 trials were assessed. With only one exception, *either no effects or only very modest changes were noted in these trials.*

- In contrast, some evidence suggests that soy foods, by inhibiting absorption, may increase the dose of thyroid hormone required by hypothyroid patients.

- In addition, there remains a theoretical concern based on in vitro and animal data that in individuals with compromised thyroid function and/or whose iodine intake is marginal soy foods may increase risk of developing clinical hypothyroidism. Therefore, it is important for soy food consumers to make sure their intake of iodine is adequate.

Even more recent… long term study of 3 years:

“These data suggest that genistein aglycone intake does not significantly increase the risk of clinical or subclinical hypothyroidism at the dose of 54 mg/d.”

But wait…

- Sixty patients with subclinical hypothyroidism. Of those, six female patients (6/60) progressed into overt hypothyroidism after 16-mg isoflavone supplementation (cross over design).
- However… systolic and diastolic blood pressure, hsCRP and insulin resistance all decreased with that 16 mg isoflavone supplementation.

The Soy/Thyroid Controversy

My take....

• Concerns are based primarily on *in vitro* research, animal studies, and older reports of goiter in infants fed soy formula not fortified with iodine.

• It is reasonable to be cautious in people with a history of thyroiditis or on a poor diet that may be marginally deficient in iodine.

• Some people are likely “thyroid sensitive” to soy protein and/or its isoflavones.

• **For the broad majority of individuals, normal dietary soy is unlikely to have any long-term negative effects on thyroid function.**
Diet: Extremes in Caloric Intake Affect Thyroid Function

• During caloric restriction
  – Serum T3 concentrations decrease as a consequence of its reduced production rate from peripheral deiodination of T4.
  – Serum RT3 concentrations markedly increase as a result of its decreased metabolic clearance rate.

• During caloric restriction and overfeeding serum T4 concentrations and its production and degradation are not modified.

Diet: Nutritional Insufficiencies

Zinc

• Supplementation resulted in increased levels of serum free T3, reduced levels of rT3 and normalised TSH levels.

• This is the likely result of zinc’s role as cofactor for the thyroid receptor.

Diet: Nutritional Insufficiencies
Selenium-dependent Enzymes and Thyroid Function

Selenium plays an essential role in thyroid hormone synthesis because two enzymes involved in thyroid hormone production are selenoproteins: the deiodinases and glutathione peroxidase.

Diet: Nutritional Insufficiencies
Selenium and Antioxidant Defenses

• The human thyroid gland contains one of the highest selenium concentrations of any tissue in the body.

• Selenium is present in thyrocytes and follicular tissue as:
  – Glutathione peroxidase
  – Selenoprotein P
  – Thioredoxin

• Extracellular glutathione peroxidase in thyroid tissue acts as an antioxidant defense system against significant amounts of hydrogen peroxide resulting from thyroid hormone production.

Diet: Nutritional Insufficiencies

Iron

• Iron deficiency impairs thyroid hormone synthesis by reducing the activity of heme-dependent thyroid peroxidase.

• Iron-deficiency anaemia blunts, and iron supplementation improves, the efficacy of iodine supplementation.

Goldilocks and the Iodine Controversy
Iodine
A Double Edged Sword

• Diets both low and high in iodine are associated with hypothyroidism.

• Studies that have shown that both low and high urinary iodine excretion are associated with hypothyroidism.

• High intake of iodine also increases the risk of Hashimoto’s thyroiditis.

Map of Iodine Deficiency

Iodine Insufficiencies and NHANES

• NHANES I (1971–1974) and NHANES III (1988–1994) showed that Americans’ median urine iodine concentration decreased by 50%, while a low urine excretory level of iodine below the WHO threshold increased by 4.5-fold in this same period.

• Monitoring of high-risk groups showed that 6.7% of pregnant women and 14.9% of women of childbearing age had a urine excretory level of less than the WHO threshold of iodine.

• The most recent NHANES (NHANES IV: 2001–2002) indicated level of iodine has stabilized since NHANES III.

Iodine Insufficiencies and Vegetarians/Vegans

• **Deficits in Vegetarians and Vegans:**
  - 172 µg/l in vegetarians
  - 78 µg/l in vegans
  - 216 µg/l in subjects on a mixed diet.

• According to this study: **25% of the vegetarians and 80% of the vegans suffer from iodine deficiency (iodine excretion value below 100 µg/l) compared to 9% in the persons on a mixed diet.**

• **Proposed link:** Prevailing consumption of food of plant origin, no intake of fish and other sea products, as well as reduced iodine intake in the form of sea salt.

Iodine excess

• Several mechanisms are involved in the maintenance of normal thyroid hormone secretion, even when iodine intake exceeds physiologic needs by a factor of 100.

• Although excess iodine exposure generally does not result in any apparent clinical consequences, thyroid dysfunction can occur in vulnerable patients with specific risk factors, including those with pre-existing thyroid disease, the elderly, fetuses and neonates.

• As iodine-induced hypothyroidism or hyperthyroidism might be either subclinical or overt.

Iodine excess and supplements

- One study noted that iodine (as potassium iodide or kelp) was a labelled ingredient in only 51% of 223 prenatal nonprescription and prescription multivitamins.

- Among the 25 brands containing iodine derived from kelp, measured values (33–610 μg per daily dose) were frequently discordant with the labelled values (75–300 μg per daily dose), including 13 brands with a >50% discrepancy between the measured and labeled values.

Iodine excess and conventional recommendations

The American Thyroid Association recommends against ingestion of an iodine or kelp daily supplement containing >500 μg iodine for all individuals, except for certain medical indications.

Additional Iodine References

Nutritional Synergies

• Studies using 50 mcg selenium daily in goiter-endemic areas in Zaire have resulted in significant improvement of symptoms, while serum levels of T4 and reverse T3 dropped to normal range, serum total T3 improved, and serum TSH levels stayed within normal ranges.

• Because of the interaction of iodine and selenium in thyroid metabolism, and the fact that iodine replacement increases oxidative metabolism in thyroid tissue, it is recommended that in situations where both selenium and iodine are deficient, replacement of both minerals is necessary for the normalization of thyroid function.


Nutritional Synergies

• Low T3/T4 ratio may be related to impaired zinc and/or selenium status.
• Supplementation was associated with modest changes in thyroid hormones, with an earlier normalization of T4 and RT3 plasma levels.


Why so much mineral deficiency?

One reason--
Topsoil Erosion

Another Reason…

Percent of U.S. Population **NOT** Meeting the Dietary Reference Intake (DRI) for Specific Nutrients

Diet: Nutritional Insufficiencies

Vitamin A Insufficiencies

Factors that either produce vitamin A (retinol) insufficiency or prevent the conversion of vitamin A to retinoic acid may result in reduced thyroid nuclear signaling.

Diet: Nutritional Insufficiencies

Vitamin D

Vitamin D Link to Autoimmune Thyroid

- VDR gene polymorphism was found to associate with autoimmune thyroid diseases (AITDs).

- The prevalence of vitamin D deficiency was significantly higher in patients with AITDs compared with healthy individuals (72% versus 30.6%; P<0.001), as well as in patients with Hashimoto's thyroiditis compared to patients with non-AITDs (79% versus 52%; P<0.05).

- Significantly low levels of vitamin D were documented in patients with AITDs that were related to the presence of anti thyroid antibodies and abnormal thyroid function tests, suggesting the involvement of vitamin D in the pathogenesis of AITDs and the advisability of supplementation.

Key Nutrients to Consider in Thyroid Dysregulation

• Zinc
• Selenium
• Iron
• Iodine
• Vitamin A
• Vitamin D
Why is there so much thyroid dysfunction?

• Stress
• Inflammation
• Infection
• Dietary factors
  – Gluten
  – Goitrogens
  – Low-calorie diet
  – Nutritional Insufficiencies
• Medications
• Toxins
Medications and Thyroid Function

Many medications affect thyroid function by blocking conversion of T4 to T3.

Diodinase Enzyme  
D1 and D2

T4

T3
Common Medications that Block Conversion of T4 to T3

- Beta blockers
- Birth control pills
- Oestrogen replacement
- Lithium
- Phenytoin
- Theophylline
- Chemotherapy
Why is there so much thyroid dysfunction?

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At least 150 industrial chemicals have been shown to result in the reduction in TSH and/or T4.

Exposure to Dioxin-like Toxic Equivalents

Antecedents, Triggers and Mediators of Thyroid Function

T4

RT3 T3

T3
Factors that contribute to proper production of thyroid hormones

- Nutrients: iron, iodine, tyrosine, zinc, selenium, vitamin E, B2, B3, B6, C, D
Antecedents, Triggers and Mediators of Thyroid Function

Factors that inhibit proper production of thyroid hormones
- Stress
- Infection, trauma, radiation, medications
- Fluoride (antagonist to iodine)
- Toxins: pesticides, Hg, Cd, Pb
- Autoimmune disease: coeliac
Antecedents, Triggers and Mediators of Thyroid Function

Factors that increase conversion of T4 to T3
• Selenium
• Zinc
Antecedents, Triggers and Mediators of Thyroid Function

Factors that increase conversion of T4 to RT3
- Stress
- Trauma
- Low-calorie diet
- Inflammation (cytokines, etc.)
- Toxins
- Infections
- Liver/kidney dysfunction
- Certain medications
Antecedents, Triggers and Mediators of Thyroid Function

Factors that improve cellular sensitivity to thyroid hormones
- Vitamin A
- Exercise
- Zinc
Factors that Affect Thyroid Function

Factors that contribute to proper production of thyroid hormones
- Nutrients: iron, iodine, tyrosine, zinc, selenium, vitamin E, B2, B3, B6, C, D

Factors that inhibit proper production of thyroid hormones
- Stress
- Infection, trauma, radiation, medications
- Fluoride (antagonist to iodine)
- Toxins: pesticides, mercury, cadmium, lead
- Autoimmune disease: Celiac

Factors that increase conversion of T4 to T3
- Stress
- Trauma
- Low-calorie diet
- Inflammation (cytokines, etc.)
- Toxins
- Infections
- Liver/kidney dysfunction
- Certain medications

Factors that improve cellular sensitivity to thyroid hormones
- Vitamin A
- Exercise
- Zinc

T4 and RT3 compete for binding sites
Nucleus/Mitochondria

“Understanding Factors that Affect the Thyroid” in your Toolkit
Assessing Low or Suboptimal Thyroid Function Clinically

- History
- Signs and symptoms
- Basal body temperature
Thyroid Questionnaire

“Put a check by the following statements that apply to your family history, your personal history, and the symptoms that you may have.”

Thyroid Questionnaire is in your Toolkit
Thyroid Questionnaire

Put a check by the following statements that apply to your family history, your personal history, and the symptoms that you may have

History
___ My family (parent, sibling, child) has a history of thyroid disease
___ I've had a thyroid problem (i.e., hyperthyroidism, Graves' disease, Hashimoto's thyroiditis, post-partum thyroiditis, goiter, nodules, thyroid cancer) in the past
___ A member of my family or I have currently or in the past been diagnosed with an autoimmune disease
___ I have had radiation treatment to my head, neck, chest, tonsil area, etc.
___ I grew up, live, or work near or at a nuclear plant
___ Women: I have a history of infertility or miscarriage

Signs and Symptoms
___ I am gaining weight for no clear reason or am unable to lose weight with a diet and exercise program
___ My "normal" body temperature is low (below 98.2°F/36.8°C when I take it)
___ My hands and feet are cold to the touch and I frequently feel cold when others do not
___ I feel fatigued or exhausted more than normal
___ I have a slow pulse, and/or low blood pressure
___ I have been told I have high cholesterol
Top 10 Signs and Symptoms that I Ask about When I Suspect Suboptimal Thyroid Function

1. Fatigue
2. Weight Gain
3. Feeling Cold
4. Dry Hair and Skin
5. Hair Loss
6. Menstrual Irregularities
7. Oedema
8. Muscle Aches and Joint Pain
9. Constipation
10. Depression
What do these symptoms make you think of?

- Hypotension
- Hypoglycemia
- Poor tolerance to stress and exercise
- Fatigue
- Hair loss
- Poor concentration
- Cold extremities
- Headaches
Assessing Metabolic Rate: Basal Body Temperature

Shake down a thermometer to below 95 degrees F/35C and place it by the bed before going to sleep.

This is not well validated but something your patients may ask you about and can be additional information (not diagnostic)

- Note: Menstruating women should record where they are in their cycle as BBT increases with ovulation.

....In your Toolkit
What do we know that causes the thyroid to go awry?
How do you recognise it clinically?
What do you test for?
How do you treat short of HRT?
Laboratory Work-Up

• TSH Myths
  – Reference range
  – Suboptimal and subclinical
  – Adequate as a screen

• Preliminary laboratory work up continued: FT3, FT4, RT3, TT3, TT3/RT3, FT3/FT4, Thyroid Antibodies

• The rest of the story
Laboratory Testing: What Specimen to Test?

Blood vs. Urine vs. Saliva

• Blood is easily available.
• Blood tests are covered by insurance.
• Blood is easier than 24-hour urine.
• Blood has more documentation than saliva or urine.
• Blood levels have been shown to be consistent markers (with notable caveats).
“Be open-minded, but not so open-minded that your brains fall out.”
Laboratory Testing: What Specific Tests to Order?

TSH: Third-generation “highly sensitive” assay:
- Sensitivity to 0.02 mIU/mL
- Upper limit: went from ~10 to ~4.5 mIU/mL in past 20 years
Laboratory Work-Up

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• Preliminary laboratory work up continued: FT3, FT4, RT3, TT3, TT3/RT3, FT3/FT4, Thyroid Antibodies

• The rest of the story
THE MYTH OF MULTITASKING

YOUR BRAIN ON ONE TASK

(HAPPY BRAIN)

YOUR BRAIN MULTITASKING

UNUSED BRAIN JUICE
Laboratory Work-Up

• TSH Myths
  – Reference range
  – Suboptimal and subclinical
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• Preliminary laboratory work up continued: FT3, FT4, RT3, TT3, TT3/RT3, FT3/FT4, Thyroid Antibodies

• The rest of the story
TSH Myth #1: The Standard Reference Range Accurately Predicts Thyroid Function

In 2002, the National Academy of Clinical Biochemistry (NACB) suggested new guidelines for the diagnosis and monitoring of thyroid disease. They said:

• TSH reference range may be too wide.
• Newer research suggested that these older ranges included individuals with borderline thyroid disease.
• When the NSAB did better screening to exclude anyone who was borderline hypothyroid, 95% of the population tested actually had a TSH level between 0.4 and 2.5 uIU/ml.
TSH Myth #1

• In NHANES III, of over 17,000 people evaluated, more then 80% had a serum TSH below 2.5 mIU/L.

• TPOAb prevalence was lowest (<3%) when TSH was between 0.1 and 1.5 mIU/liter in women and between 0.1 and 2.0 mIU/liter in men and progressively increased to above 50% when TSH exceeded 20 mIU/liter.

• Their conclusions: TSH upper reference limits may be skewed by TPOAb-negative individuals with occult autoimmune thyroid dysfunction.


Our data indicate that each individual had a unique thyroid function. The individual reference ranges for test results were narrow, compared with group reference ranges used to develop laboratory reference ranges. Test results within laboratory reference limits is not necessarily normal for an individual. Just because a test result is somewhere within the laboratory reference range does not necessarily mean it is optimal for that individual.

Anderson et al., "Narrow Individual Variations in the Serum T4 and T3 in Normal Subjects: A Clue to the Understanding of Subclinical Thyroid Disease," *Journal of Clinical Endocrinology and Metabolism*, 2002; 87(3): 1068-1072
TSH Myth #1 is ongoing
Most conventional labs and mainstream clinicians have not adopted these new recommendations, and debate continues.
Conclusions about TSH

1. The Conventional RR is too wide. Optimal RR should be: 0.4 - 2.0/2.5

TSH Myth #2: “Subclinical” Hypothyroid should not be treated

Standard definitions:

• “Clinical Hypothyroid”: High serum thyrotropin (TSH) concentration and a low serum free thyroxine (T4) concentration

• “Subclinical Hypothyroid” (SCH): Normal free T4 (FT4) in the presence of an elevated TSH concentration
We shouldn’t ask what is ‘Subclinical’ but What is Suboptimal?
What’s the Evidence?

Patients with SCH have a high rate of progression to clinically overt hypothyroidism:

– 2.6% each year if thyroperoxidase (TPO) antibodies are absent
– 4.3% each year if thyroperoxidase (TPO) antibodies are present

Replacement in SCH resulted in:
- decreased total cholesterol, non-HDL cholesterol, and apolipoprotein B
- decreased arterial stiffness
- decreased systolic blood pressure


What’s the Evidence?

“Treatment of subclinical hypothyroidism reduces serum cholesterol and has the potential to reduce cardiovascular mortality risk by up to 31%.”

More Recent Evidence

Six recent meta-analyses suggest that SCH is associated with…

- A cardiovascular risk for persons younger than age 70
- No effect for those aged 70 to 80
- A possible protective effect for those older than 80

Biondi B. Cardiovascular effects of mild hypothyroidism. Thyroid 2007;17(7):625-630.
To be (relatively) balanced...

2007 meta-analysis of 14 randomised clinical trials...replacement therapy for SCH does not result in improved survival or decreased CVD morbidity...Data on health-related quality of life and symptoms did not show significant differences between intervention groups.... But some evidence indicates *T4 replacement* improves some parameters of lipid profiles.

What to do?

• The American College of Physicians recommends that women over 50 years old be screened for thyroid disorders every 5 years.

• The American Academy of Family Physicians believes that adults do not have to be screened until they are over 60.

• The American Thyroid Association recommends that all adults, both men and women, begin their screening at age 35 and every 5 years thereafter.

• The U.S. Preventive Task Force recommends against routine screening for thyroid disease in adults.
Conclusions about TSH

1. The RR is too wide: Optimal RR should be 0.4 - 2.0/2.5

2. Suboptimal TSH is likely to differ from individual to individual. In a patient with suggestive signs/symptoms, testing for thyroid dysfunction is important and we should use a TSH within the optimal RR as (but) one guideline.
TSH Myth #3

*TSH can be used as the sole diagnostic criterion for thyroid dysfunction*
Is TSH the Ultimate Diagnostic Criterion?

• Can TSH reflect variations in target cell sensitivity (thyroid resistance), where cells fail to respond properly to these hormones?
• Can TSH reflect peripheral T4 to T3 conversion dysfunction?
• Can TSH reflect cellular transport problems where there is faulty transport of T4 or T3 into mitochondria?
• Can TSH reflect displacement of thyroid hormones from cellular receptors by RT3, antithyroid antibodies, or other substances?
Is TSH the Ultimate Diagnostic Criterion?

• Testing TSH indicates only pituitary production.
• Both genetic and environmental factors can effect TSH secretion.
• Pituitary hormone levels alone are not sufficient to measure the function of the gland they regulate.
Is TSH the Ultimate Diagnostic Criterion?

“TSH reference ranges may in fact be but a crude parameter for detecting disease in an individual patient and we should not be confusing a population reference range with an individual’s ‘normal range’.”

The European Thyroid Association doesn’t think so…

“Because of tissue heterogeneity, pituitary TSH secretion may not reflect what happens in other target tissues, and therefore serum TSH alone may not be a good marker for the adequacy of thyroid hormone replacement.”

Conclusions about TSH

1. The RR is too wide: Optimal RR should be 4-2.0/2.5

2. Suboptimal TSH is likely to differ from individual to individual. In a patient with suggestive signs/symptoms, testing for thyroid dysfunction is important and we should use a TSH within the optimal RR as (but) one guideline.

3. Using only TSH is not adequate to assess suboptimal thyroid function.
References


Explaining all this to the patient

“Understanding Thyroid Testing” in your Toolkit
Laboratory Work up

• TSH Myths
  – Reference range
  – Suboptimal and subclinical
  – Adequate as a screen

• Preliminary laboratory work up continued: FT3, FT4, RT3, TT3, TT3/RT3 FT3/FT4, Thyroid Antibodies

• The rest of the story
Laboratory Testing: What Specific Tests to Order?

T3 and T4: total or free hormones?

- 99% of thyroid hormones are bound to protein and are therefore inactive.
- Only 1% of circulating thyroid is free to “work.”

- The first tests of these hormones were insensitive and measured both free and bound: “TOTAL.”
- New assays are now sufficiently sensitive to measure only “FREE” hormone.
Is it necessary to test T4 and T3?

Conventionally it is thought that it’s only necessary to test for T4, as T4 is converted to T3.

However, this is true only if T4 is converted to T3 at a consistent rate in all individuals.
Do normal TSH and T4 levels actually reflect normal serum T3?

• Patients with no functioning thyroid gland (Athyreotic n=1811) on T4 replacement and having a maintained normal TSH (.4-4.0 mU/L)

• Patients with normally functioning thyroid (Control group n=3875) with no thyroid antibodies and with normal TSH (.4-4.0 mU/L)

Data from the study

- Control group
  - Median TSH 1.4
- Patients on replacement
  - Median TSH 1.2

However, in the patients on replacement...

- 15.2% were below the normal RR for Free T3
- 29.6% were below the normal range for FT3/FT4 (defined as less then 2SD from the control group)
Figure 1

FT3/FT4 ratio frequency distribution.

FT3 and FT4 serum levels and FT3/FT4 ratio distribution in 1,811 athyreotic patients under levothyroxine (L-T4) monotherapy. Shaded areas indicate the normal range (2.5–97.5 percentiles) calculated in 3,875 euthyroid controls. Vertical dotted lines indicate the median of the normal values. Percentages indicate the patients with values under or above the normal values.
Conclusions:

“…a subset of patients … do not reach a serum FT3/FT4 ratio within the reference range observed in euthyroid controls. These patients, therefore, *live in a chronic condition of abnormal thyroid hormone availability for the peripheral tissues, even if the administered levothyroxine dose is able to maintain the serum TSH within the normal range.*”

Conclusions:

“The insufficient T3 peripheral production cannot be appropriately corrected by increasing levothyroxine dose because the inhibitory effect of elevated T4 on type II deiodinase will end up increasing the imbalance of the circulating FT3/FT4 ratio.”

Conclusions:

1. T4 may be normal, but serum levels of T3 may be abnormally low in a subset of patients, suggesting that there is uneven conversion among patients from T4 to T3.

2. TSH may be normal, but serum levels of T3 may be abnormally low in a subset of patients, suggesting that T4 may be giving signals to the pituitary that do not reflect serum T3 (or intracellular T3) levels.

3. TSH and T4 may be normal but the ratio of FT3/FT4 may be abnormally low, suggesting again that TSH and T4 alone do not reflect adequacy in thyroid metabolism for a subset of patients.

So We Must Check Ability to Convert T4 to T3
T4 Conversion to T3

Prime ring

T4: HO--O--CH2–CH- C00H

Deiodinase (D1 and D2)

T3: HO--O--CH2–CH- C00H

Prime ring
Support for this Concept from the European Thyroid Association

“Theoretically, thyroid hormone replacement therapy should aim not only at normalisation of serum TSH but also at normalisation of serum free T4, free T3 and free T4/free T3 ratio.”

Another Option for T4 Metabolism:

• T4 can be metabolised by Deiodinase Type 3 (D3).
• A different iodine is removed from the other ring (the 5-locus), which converts it to RT3 (3,3',5' triiodothyronine).
• 95% of circulating RT3 is made this way.

T4 converts into both T3 and RT3

RT3: HO -- □ -- O -- □ -- CH₂ - CH - COOH
  Prime ring

Deiodinase D3

T4: HO -- □ -- O -- □ -- CH₂ - CH - COOH
  Prime ring

Deiodinase D1/D2

T3: HO -- □ -- O -- □ -- CH₂ - CH - COOH
Prime ring
Therefore…

• Converting T4 to T3 is optional.
• The body determines whether it will convert T4 to T3 or RT3.
• Our body has the option to increase or decrease its metabolic rate.
• We have another way to regulate energy use.
Function of RT3:

- RT3 was discovered in 1975 and found incapable of increasing cell metabolism (unlike T4, T3, and T2). So RT3 has been considered “functionless,” and it has been assumed that RT3 is inactive.
- It was thought that RT3 was a “default” position into which unwanted T4 is dumped without increasing metabolism.
- But RT3 does seem to be useful when a slower metabolism is advantageous: life-threatening illness, injury, or starvation.
What happens in Euthyroid Sick Syndrome?
Why couldn’t this happen on a continuum?
RT3 and Impaired Thyroid Hormone Metabolism

• RT3 is a protective/adaptive response during periods of significant stress. A slow metabolism is energy-efficient.
  – Example: RT3 lets a person live longer without food or water.

• It is not usually helpful to keep a slow metabolism. Our body’s protective, or adaptive, responses become harmful or “maladaptive” if continued for too long or if used at the wrong time.
The fate of T4 determines the rate of metabolic activity

T4

D1 and D2

D3

T3

D3

RT3

D1

T2 (inactive)

T2 (inactive)

What are D1/D2 inhibitors that slow the conversion of T4-T3?

- Certain medications
- Selenium deficiency
- Inadequate protein, excess carbohydrates
- Chronic illness (cytokines, free radicals)
- Compromised liver or kidney function
- Cd, Hg, Pb, herbicides, pesticides
- Stress (emotional or physiological), i.e., excess cortisol, catecholamines
- Excess oestrogen
- RT3
What I say to my patients…
RT3 and Impaired Thyroid Hormone Metabolism

- RT3 can effectively block enzymatic conversion of T4-T3
- Consequences:
  - One can have excessive RT3 levels with potentially normal T3.
  - Since T4 may be available but converting to RT3, symptoms of hypothyroidism can develop with normal TSH and T4 levels.
  - Low thyroid hormone effect—even with “normal” thyroid levels.
RT3 and Impaired Thyroid Hormone Metabolism

- Excessive conversion of T4 to RT3 may cause failure of “classical” thyroid treatment using T4—resulting not in low T3 but poor T3-RT3 ratio.

- The “normal” amount of T3 produced is not adequate to overcome the inhibitory effects of RT3.
RT3 and Impaired Thyroid Hormone Metabolism

This concept has been overlooked because of:

– Ignorance about RT3 function
– Dogma that T4 will always be converted adequately to T3
– Reliance on TSH as sole diagnostic criteria
Testing Reverse T3

Reverse T3 (RT3) is an important marker for reduced metabolic rate as an adaptive response and during times of stress.
Testing Total T3

• Free T3 is the most accurate measure of T3 but…

• Total T3 has been used as a measure of activity of T3 and RT3. Thus a surrogate marker of D1 and D3 activity is the TT3/RT3 ratio.

• Significant literature looking at this ratio (TT3/RT3) in animals and severely ill patients.
What should that ratio be?

- Alan McDaniel MD has developed a range for optimal function in sick ambulatory patients using his clinical experience and suggesting that t3 should be 10x RT3 based upon the level ‘normally’ excreted from the thyroid gland.
  
  McDaniels, 14th Symposium on Functional Medicine, Florida 2007

- Ken Woliner MD has developed a range for optimal function based upon the midpoint of the reference range.
  
  Woliner, personal communication 2011

I will give you these numbers on a summary slide at the end of the lecture.
Selected References on TT3/RT3 Ratio


- Peeters, RP et. al. Reduced Activation and Increased Inactivation of Thyroid Hormone in Tissues of Critically Ill Patients. J Clin Endo & Metabolism, 88(7): 3202-3211.


One Caveat about Reverse T3?
Why are you braking?
Sometimes you do want to STOP
Therefore, there are two important reasons to go beyond T4:

• Is T4 converting to T3 (in the serum) and therefore (you assume) driving the metabolic machinery of the cell?

To know, you must assess T3 and the ratio of T3/T4

• Has too much T4 been converted to RT3 --and therefore even with normal T3 serum levels there may be a metabolic block to its action?

To know, you must assess RT3 and the ratio of T3/RT3
What about Thyroid Antibodies? Should we test for them?

- It is the most common autoimmune disease in the United States.
- It is the most common cause of hypothyroidism in the United States.
- It affects women seven times more than men:
  - Up to 20% of menopausal women
  - Up to 24% of allergic women
  - 5–10% of postpartum women
Why we should test for thyroid antibodies

- 426 euthyroid female patients with normal TSH (mean between 1 and 2)
- Women with high TPO antibodies had significantly higher incidence of dry hair, chronic fatigue*, “becoming easily fatigued”, chronic weakness, dysphagia*, irritability*, lack of concentration and chronic nervousness* and lower QOL on SF 36.
- TPO antibodies were highest in patients with six or more symptoms and those with the highest BMI.
- Higher TPO antibodies were also associated with early pregnancy loss, higher age at menopause, higher gravidity, and breast cancer.

Why we **should** test for thyroid antibodies

- Symptoms consistent with Fibromyalgia (FM) were reported in almost one third of patients suffering from Hashimoto’s Thyroiditis with or without mild sub clinical hypothyroidism
- This data supports the hypothesis that thyroid autoimmunity per se plays a role in the development of FM comorbidity


Why we should test for thyroid antibodies

- 21 patients Euthyroid Hashimoto's Thyroiditis (normal range TSH, but elevated antibodies) treated
  - Half treated with levothyroxine for a year, the other half were not treated.
  - the antibody levels and lymphocytes (evidence of inflammation) decreased significantly only in the group receiving the medication.
  - Among the untreated group, the antibody levels rose or remained the same.

- Preventative treatment of normal TSH range patients with Hashimoto's disease reduced the various markers of autoimmune thyroiditis

Autoimmune Thyroid Disease is known to follow:

- Radiation exposure
- Bacterial infections and perhaps viral infections as well
- Toxic exposure
- Coeliac, Type 1 Diabetes and other autoimmune diseases
- Pregnancy
Individuals with Hashimoto’s had almost a 15% chance of having a second autoimmune disease

Summary: What to Test as Baseline

- TSH, FT4, FT3, RT3, Total T3
- Thyroid Antibodies
  - TPO Antibodies
  - Anti-TG antibodies
## Reference Ranges & Optimal Ranges

<table>
<thead>
<tr>
<th>Optimal Range Range</th>
<th>Standard Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH: 0.4-2/2.5 mIU/L</td>
<td>(rr 0.4-5.5)</td>
</tr>
<tr>
<td>Free T4: 15-23 pmol/L</td>
<td>(rr 9-23)</td>
</tr>
<tr>
<td>Free T3: 5-7 pmol/L</td>
<td>(rr 3-7)</td>
</tr>
<tr>
<td>Total T3: 120-181 ng/dl</td>
<td>(rr 76-181)</td>
</tr>
<tr>
<td>RT3: 11-18 ng/dl</td>
<td>(rr 11-31)</td>
</tr>
<tr>
<td>Ft3/Ft4: &gt;.33</td>
<td></td>
</tr>
<tr>
<td>T3/RT3: &gt;6</td>
<td></td>
</tr>
<tr>
<td>Thyroid Antibodies: negative</td>
<td></td>
</tr>
</tbody>
</table>
Laboratory Work up

• TSH Myths
  – Reference range
  – Suboptimal and subclinical
  – Adequate as a screen

• Preliminary laboratory work up continued: T3, T4, RT3, TT3, TT3/RT3, Thyroid Antibodies

• The rest of the story
Other Laboratory Assessment

• Iron:
  – CBC and Ferritin
  (Generally part of a standard work up)
• Zinc
  – RBC Zinc
  (Often order but usually find it within RR and will often just supplement)
• Selenium
  – RBC selenium
  – Whole blood glutathione
  (Rarely order, almost invariably supplement)
• Vitamin D
  – 25 OH
  (Generally part of a standard work-up)
• Vitamin A
  – (Rarely order, often supplement in suspected individuals)
Other Laboratory Assessment

• Iodine
  – Urinary iodine
  (often order a fasting spot iodine initially)

• Coeliac Panel
  – Standard panel PLUS IgG gliadin
  (often order initially, will always order with elevated antibodies and diagnosis of Hashimoto’s or Graves’)

• Food Sensitivities
What do we know that causes the thyroid to go awry?
How do you recognise it clinically?
What do you test for?
How do you treat short of HRT?
Treatment

• **Nutrition:** Review nutrient needs for optimal function.
  • Production of T4 and T3
  • Conversion of T4 to T3

• **Toxins:** Eliminate or decrease toxins and medications that affect thyroid function.
Treatment

• **Comorbidities:** Improve or minimise disease states that affect thyroid function
  - Assess and treat for Coeliac Disease (and other autoimmune conditions)
  - Assess and treat for infections and/or inflammatory conditions
  - Assess and treat for food sensitivities

• **Lifestyle:** Decrease chronic stress
  - Regular sleep
  - Exercise
  - Relationships
  - Meditation, prayer, spiritual practice, etc.
Treatment: Thyroid Replacement Therapy

- Levothyroxine
- Liothyronine
- Standardised porcine thyroid glandular
  - 4 parts T4:1 part T3
- Compounded thyroid replacement
  - Various ratios of T4 to T3
Overall Treatment Strategies

• Foundational:
  – Dietary/Lifestyle changes to remove triggers and/or address mediators
  – Supplementation

• Hormone Replacement
Lifestyle Treatments

- Sleep
- Exercise
- Community
- Stress Reduction techniques
Dietary/Lifestyle changes to remove triggers and/or address mediators

- Food sensitivities spectrum
- Gut dysbiosis
- Overall inflammation
A dietary program focused on eliminating potential food reactions, improving gut dysbiosis, and lowering inflammation should be:

- Low in potential foods that could cause reactions
- High in pre and probiotic foods
- High in phytonutrient content
- Low in the Omega-6/Omega-3 ratio
- Low in saturated and trans fatty acids
Primary Therapeutic Dietary Interventions: The Elimination Diet

- Identifies Food Triggers
- Reduces Inflammation
- Repairs Intestinal Permeability
- Promotes Body Awareness to Foods
- No Calorie Restriction
- Personalized Diet Approach
- Reduces Toxic Burden
- Phytonutrients to Heal the Gut
If the dietary focus is more on Glycemic Load and less on Food Sensitivities, consider

The Cardiometabolic Food Plan
Primary Therapeutic Dietary Interventions: The Cardiometabolic Food Plan

- Modified Mediterranean Approach
- Low Glycemic Index and Load
- Low in Simple Sugar
- Balanced Fats
- Meal Timing
- High in Fiber
- Targeted Calories
- Therapeutic Foods
- Low in Simple Sugar
- Modified Mediterranean Approach

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If Toxins are a Primary Issue...
...then focus on eliminating or decreasing toxins that affect thyroid function

• Assess for **toxins** and decrease/eliminate if possible

• Assess for and eliminate **medications** (as possible) that inhibit function

• Improve the **dietary prescription** with a focus on detoxification/biotransformation
Therapeutic Dietary Interventions: The Detoxification Food Plan

- Reduces Known Food Triggers
- Balances Hormone Metabolism
- High Fiber for Optimal Elimination
- Fasting and Calorie Options
- Adequate Protein to Aid Detox
- Choose Clean and Organic Foods
- Phytonutrients for Gut, Liver, and Kidney
- Targeted Anti-oxidants
Functional Nutrition Dietary Interventions

**Functional Nutrition Fundamentals**
- Foundational Diet
- Quality and Quantity
- PFC-MVP
- Phytonutrients
- Mindful Eating

**First Step Dietary Interventions**
- Core Food Plan
- Elimination Diet
- Cardiometabolic Food Plan

**Advanced Therapeutic Interventions**
- GI Specific Plans
- Detox Food Plan
- Energy Food Plan

Transitioning Process
Functional Nutrition Dietary Interventions

Functional Nutrition Fundamentals
- Foundational Diet
- Quality and Quantity
- PFC-MVP
- Phytonutrients
- Mindful Eating

First Step Dietary Interventions
- Core Food Plan
- Elimination Diet
- Cardiometabolic Food Plan

Advanced Therapeutic Interventions
- GI Specific Plans
- Detox Food Plan
- Energy Food Plan

Personalized Nutrition Plan
Taking a patient through each of these plans is detailed in a series of webinars that will be placed in your ‘my courses’ content folder and available following the onsite program.
Treatment Strategies

• Foundational:
  – Dietary/Lifestyle changes to remove triggers and/or address mediators
  – Supplementation

• Hormone Replacement
Key Nutrients to Consider in Thyroid Regulation

- Selenium
- Zinc
- Iron
- Iodine
- Vitamin D
- Vitamin A
Routine Daily Supplementation in a hypothyroid patient

- **Selenium**: 200-400 mcg
- **Zinc**: 15-30 mg
- **Vitamin D**: 2000 iu
- **Vitamin A**: 2000 iu
- **Iodine**: 150 mcg
- **Iron**: 15-20 mg (in a menstruating woman)

(Generally all can be given in one or two supplements)
Generally requires further testing

• Iron supplementation above RDA
  – to achieve a ferritin of 50-100
• Iodine supplementation above 500 mcg
  – To achieve a urinary first morning iodine above 150
• Vitamin D supplementation above 2000 iu/day
  – To achieve 25 OH vitamin D 50-80
Watch out for supplements “with a kick”

• Researchers tested 10 popular thyroid supplements sold online and found that 9 contained either T4, T3 or both

• Taken at the recommended dose:
  – 5 supplements delivered T3 at greater than 10 μg/day
  – 4 delivered T4 ranging from 8.57 to 91.6 μg/day

“It is much more important to know what sort of person has a disease, than what sort of disease a person has.”

William Osler, MD