Hypothyroidism, Functional Hypothyroidism, and Functional Hypometabolism

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ZRT Laboratory is a testing Laboratory for hormones, cardiometabolic risks factors, Vitamin D
Less Than Optimal Thyroid Function

• 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
  – Problems with intracellular transport
Subclinical Hypothyroidism

- Thyrotropin (TSH) elevated with normal thyroxine (T4) and triiodothyronine (T3) levels
- Patient symptomatic
- Has been considered compensated or euthyroid and no requirement for treatment
Subclinical Hypothyroidism

• Plethora of studies have demonstrated Subclinical Hypothyroidism often associated with significant symptoms and increased risk for morbidity and mortality

• More appropriate term: Mild Thyroid Failure (MTF)

Mcdermott M.T., Ridgway C.: Subclinical hypothyroidism is mild thyroid failure and should be treated. J Clin Endocrinol Met 86. (10): 4585-4590.2001;
Mild Thyroid Failure

• MTF is associated with a 2.2 fold increased risk of coronary artery disease and 1.5 fold increase in risk of cardiovascular mortality

• Treatment can result in:
  – Significant reduction in cholesterol levels
  – Lowering risk of arthrosclerosis, myocardial infarction, coronary artery disease and cardiovascular mortality

• Treatment warranted despite normal TSH and T4 levels
Thyroid Gland

TRH + Pituitary Gland

TSH +

Thyroid Gland

T4

T3

Effects On Body (Symptoms)

Thyroid receptor in tissue cells
Thyroid Gland

Pituitary Gland

TRH +

TSH +

Thyroid Gland

T3

T4

Hypothyroidism
Thyroid Gland

TRH + Pituitary Gland

+ TSH

Thyroid Gland

TSH +

T4 ↓

×

Functional Hypothyroidism

T3

↓ ×

fT3

×
Thyroid Gland

Effects On Body
(Symptoms)

Functional Hypometabolism

Thyroid Hormone Resistance

Thyroid receptor in tissue cells

TRH + Pituitary Gland

TSH + Thyroid Gland

T4

T3

T4

T3
Causes of Overt Hypothyroidism

• Thyroid function decreases with age
  – Two – to threefold increase in incidence with age
  – Decrease production occurs at ages 45-50 in normal individuals

• Lack of components that make up thyroid hormones
  – Iodine
    • Lack of iodine causes increase in size of thyroid gland
  – Tyrosine
    • Watch in Vegans, Vegetarians and Body Builders
Causes of Overt Hypothyroidism

• “Sluggish” thyroid – poor recovery following acute stress
  – Acute stress shuts down thyroid function
  – Thyroid gland fails to bounce back after stress is relieved
  – Look for acute stressor 6-18 months prior to onset of symptoms

• Thyroid Gland destruction
  – Autoimmune reaction, heavy metal toxicity
  – Cells of gland destroyed
  – Will most often need TRT
Causes of Functional Hypothyroidism

- Excessive binding of thyroid hormones due to increased TBG caused by
  - Estrogen dominance and/or therapy
    - Pregnancy, OCs, ERT (especially oral)
  - Thyroid replacement therapy
  - Delayed response
    - 2-3 months for net effect
  - Chronic sleep disturbances

- Note: decreased TBG/binding reported:
  - Androgens, glucocorticoids, Phenytoin, salicylates, malnutrition
Binding of Thyroid Hormones

• More than 99% of circulating thyroid hormones are bound to serum proteins
  – Thyroxine-binding globulin (TBG)
  – Thyroxine-binding prealbumin (TBPA)
  – Albumin (TBA)

• T4 is more extensively bound than T3
  – 0.04% of total T4 if free
  – 0.4% of total T3 is free

• A small difference in TBG can have a major effect on the percentage of unbound hormone
Causes of Functional Hypothyroidism

• Decreased conversion of T4 to T3
  – Creates imbalance of fT3 and rT3
Normal T4 Conversion to T3 by the Enzyme 5’deiodinase.

- **T3** (Triiodothyronine, Active)
- **T2** (Active?)
- **T4** (Thyroxin, Inactive)
- **rT3** (Reverse T3, Inactive – Binds to T3 receptors)
T4 to T3 Conversion

• Whenever T4 is administered, you are depending on proper conversion to T3 to obtain desired metabolic effects!
De-Iodinases

- **D1** in liver & kidneys
  - Systemic T3 production
- **D2** in muscle, & in brain & pituitary
  - Local T3 production
- **D3** in brain
  - T4, T3 degradation

- Extrathyroidal T3 production is mediated primarily by type D2 normally
  - At low & normal T4, D2 predominates (muscle)
  - At high T4, D1 predominates
Inhibition of T4 Conversion to T3 by the Enzyme 5’déiodinase.

- **T4** (Thyroxin, Inactive) is converted to **T3** (Triiodothyronine, Active) by 5’deiodinase.
- **T3** can also be converted back to **T4** by 5’deiodinase.
- **T2** (Active?) is produced from **T3** and can be converted to **rT3** (Reverse T3, Inactive – Binds to T3 receptors).
- **rT3** is converted back to **T3** by 5’deiodinase.
Factors That Inhibit T4 to T3 Conversion

Nutrient Deficiencies

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

David Brownstein, MD (adaptation)
Factors That Inhibit T4 to T3 Conversion

- Stress (high cortisol)
- Aging
- Alcohol
- Obesity
- Chemotherapy
- Cigarette Smoking
- Diabetes
- Fasting
- High reverse T3
- Kidney & Liver Disease
- Starvation

- Mercury
- Lead
- Growth Hormone Deficiency
- Hemochromatosis
- Pesticides
- Radiation
- Surgery
- Soy*
- Cruciferous Vegetables*

*excessive amounts

Adapted from David Brownstein, MD
Factors That Inhibit T4 to T3 Conversion

Medications

- Glucocorticoids
- Beta Blockers
- Low Progesterone
- SSRIs
- Too much Iodine
- Opiates
- Phenytoin
- Chemotherapy
- Theophylline
- Lithium
Treatment of Poor Conversion

• Address stressors and stress reaction
• Check for heavy metal toxicities
• Fix nutritional deficiencies
  – Use of good nutritional MVM
  – Additional Selenium up to 400mcg total daily
  – Additional Zinc (good chelate) to 25-50mg daily
  – If IR present, additional Chromium up to 400mcg daily
• Remove other factors and medications as necessary if possible
Thyroid Gland

TRH + Pituitary Gland

TSH +

Thyroid Gland

T4

T3

Effects On Body (Symptoms)

Functional Hypometabolism

Thyroid Hormone Resistance

Thyroid receptor in tissue cells X
Functional Hypometabolism
(Thyroid Hormone Resistance)

- Thyroid levels are optimal in values and in relationship to each other, but **symptoms persist**
  - Adequate production & metabolism

- Thyroid receptor not responding to optimal thyroid levels
  - Target tissues of the body have reduced responsiveness to thyroid hormone
Causes of Functional Hypometabolism

• Vitamin D level below optimal
  – Affects thyroid receptor response (Jeffrey Bland, PhD)
  – Low end of serum level range should be 32 (not 15)
  – Optimal range for thyroid receptor function is 60-80
Vitamin D Dosing

• Always use Vitamin D3
  – Good nutritional company brand

• If levels are below 30, 10,000 Units daily for 2-4 weeks, then 5000 U daily

• If levels are normal but sub optimal (30-59), 2000-4000 U daily

• Retest in 2-3 months and adjust dose prn
Causes of Functional Hypometabolism

• Low ferritin
  – Required for transport of T3 to nucleus of cell and utilization of hormone
  – Optimal level for thyroid function is 90-110
Ferrous Glycinate

- Ferrous glycinate is iron replacement therapy with better absorption than other forms of iron
  - Give with Vitamin C to maximize absorption
  - Does not cause constipation
  - Known also as bisglycinate or iron glycinate
  - Dose at 50 to 200 mg of elemental iron daily
    - Keep at least 4 hours from any TRT
    - If ferritin level low (10-40) it will may take many months at 50 mg daily to raise level
    - Dose at 100 mg elemental iron daily to raise level more quickly. Increase up to 200 mg daily prn
Causes of Functional Hypometabolism

- **Genetic** anomalies of thyroid hormone receptors
- Autoimmune (antibodies), oxidative, or toxic **damage** to thyroid-hormone receptors
  (heavy metal toxicities)
- **Competitive binding** to thyroid-hormone receptors by pollutants, food additives, etc.
  (halogens, pesticides, perchlorate)
Causes of Functional Hypometabolism

- Excessive competitor to T3
  - T3 receptor forms a heterodimer with RXR
  - Progesterone, Vitamin D, and ω3 fatty acids also form heterodimers with RXR
  - Excess of any can block signaling of the others
Vitamin D, T3, fatty acids and progesterone can all compete with each other through this mechanism.
Stress and the HPT Axis

Hypothalamus → TRH → Pituitary

Stressors → CRH → Cortisol ↑

Pituitary → TSH → Thyroid Gland

Thyroid Gland → T4

T4 → Reverse T3 ↑, Active T3 ↓

Thyroid Receptor
Causes of Functional Hypometabolism

- **Excess cortisol**
  - Inhibits T4 to T3 conversion
  - Suppresses TSH
  - Decreases thyroid receptor responsiveness

- **Low cortisol**
  - Decreases thyroid receptor responsiveness
  - May inhibit T4 to T3 conversion
  - Transport across the membrane is energy dependent & modified by cortisol
  - Cortisol regulates T3 receptor density
  - May have to give cortisol to make thyroid supplementation work properly
• You must address adrenal dysfunction before fixing the thyroid function
  – High cortisol: causes excess catabolic action on muscles and bones
  – Low cortisol: adrenal insufficiency cannot meet the demands of increased metabolism
  • Hypoadrenalism is an absolute contraindication to thyroid replacement therapy
Considerations in Thyroid Testing
"Are not the feelings of the patients often as clinically valuable as the other findings? In no case can we wholly discount them. A good laboratory report is cold comfort to a patient whose symptoms remain unchanged, and the doctor can repeat such reports until he is blue in the face, but they will not help his patient much if unaccompanied by controlled symptoms and changed feelings. The successful physician is the one who knows best how to make his patients feel better."

Henry Harrower, M.D. *Endocrine Fundamentals* 1931
Optimal Thyroid Levels?

Number of People

Optimal Thyroid Function

Level
TSH

- Test designed as a screening tool only not diagnostic or therapeutic measurement
  - Not VALIDATED in to use to judge effectiveness or TRT
  - Not VALIDATED to use to adjust dosage
TSH

• TSH can often be misleading and unreliable
  – Assumes that hypothalamic-pituitary function is intact and normal
  – Assumes that the patients thyroid status is stable, i.e. the patient has had no recent therapy for hypo-or hyperthyroidism
• Thyrotropin test is unreliable with significant stress, illness, inflammation, aging, chronic physiological stress, and calorie reduction
  – Significantly diminished thyroid levels in peripheral tissues no longer correlate with TSH levels
  – TSH cannot be relied in for accurate measure of tissue thyroid effect
T4 Serum Levels

• With stress, illness, inflammation and aging, tissue-specific alterations:
  – Suppressed T4 levels due to suppressed TSH
  – Reduced tissue T3 levels
    • Reduced T4 uptake into tissue cells and
    • Decreased T4 to T3 conversion
  – The correlation between serum T4 and TSH and peripheral thyroid activity no longer follows

• T4 levels of little use in most cases
TSH and T4 Serum Levels

- With stress, illness, inflammation and aging,
  TSH and T4 levels cannot be relied on to detect decreased cellular T3 levels.
Reverse T3

• With stress, illness, inflammation and aging, T4 is preferentially converted to reverse T3

Serum reverse T3 levels can be useful because of inverse correlation to diminished cellular uptake of T4, decreased conversion to T3, and decreased cellular T3 levels.
Adequate Testing

• In patients having symptoms consistent with hypothyroidism but normal TSH and T4 levels, obtaining fT3, rT3 and fT3/rT3 ratios may help obtain a more accurate evaluation of tissue thyroid status and may be useful to predict those who respond favorably to T3 supplementation.

Thyroid “Panel”

- TSH, TT4, RT3U or T3U(T3 resin uptake), and Free Thyroxine Index (FT4I)
- Total T4
  - May be normal, but not enough converted to T3
- T3 resin Uptake
- Does not measure Free T3 levels
- *Estimates* the amount of unbound TBG.
  - How much binding sites are available
  - Low T3 uptake = lots of T3 - few empty binding sites and high T3 uptake = low T3 (lots of spaces available)
- Free Thyroxine Index (FT4I)
  - *Calculation based on an estimate* of serum free T4
    - Multiple T4 by T3 uptake
    - Calculated from total T4 and thyroid hormone binding ratio
- T3 uptake and FTI cheaper than measuring actual free T3 and rT3 hormone levels
Thyroid Level Gradients

TT4
Low                 Low
Mid
High

FT4
Low                 Low
Mid
High

FT3
Low                 Low
Mid
High

rT3
Low                 Low
Mid
High

Lab Range

Patients Value
Thyroid Level Gradients Example

TT4
11.2

4.4 12.5
Thyroid Level Gradients Example

TT4
- 11.2
- 4.4
- 6.25
- 8.45
- 10.475
- 12.5

fT4
- 1.48
- 0.73
- 1.34
- 1.95

rT3
- 317
- 90
- 155
- 220
- 285
- 350

fT3
- 2.5
- 2.3
- 3.25
- 3.725
- 3.775
- 4.2
Conversion of T4 to T3

Conversion of T4 to T3

ft4
1.035
1.645
0.73
1.95

ft3
2.775
3.725
2.3
4.2

ft4
3.25

ft3
Free $T_3$ and $rT_3$

- If the conversion of T4 to FT3 and rT3 is normal, FT3 and rT3 should have about the same position on the clock.
- Even though $rT_3$ is within the normal range for this laboratory, it is in excess of FT3.
- Since FT3 and rT3 occupy the same receptor and FT3 will activate the receptor and rT3 will not, if the patient has excess $rT_3$ they will have symptoms of tissue hypometabolism despite all the laboratory tissue falling within the normal range.
Thyroid Level Gradients Example

- **rT3**
  - 90: 2.3
  - 350: 3.725

- **TT4**
  - 4.4: 6.25
  - 12.5: 10.475

- **fT4**
  - 0.73: 1.035
  - 1.95: 1.645

- **fT3**
  - 2.3: 2.775
  - 4.2: 3.725

- **rT3**
  - 90: 317
  - 350: 285
High T3s

T3s high relative to corresponding T4s

Check for autoimmune or toxicity problem
Thyroid Testing

**Initial** testing:

• Patients < 45 yo and/or on thyroid replacement
  – TT4, fT4, fT3, TPO, TSH
    • Antibodies are the most frequent cause of thyroid conditions

• Patients with chronic symptoms, non-responsive to therapy
  – TSH, TT4, fT4, fT3, TPO, ferritin, Vit. D, Iodine
  – Reverse T3?
Thyroid Testing

Follow-up testing

• fT4, fT3, TPO, TSH
  – Add ons - where previous testing or dosage adjustments indicate need to monitor:
    • Ferritin
    • Vitamin D
    • Iodine
Interpretation of Testing

- **Timing** of sample in relationship to last dose of TRT is **critical** to interpretation of results.

- For correlation of levels to TRT you want to avoid peaks and valleys

- Keep timing consistent in follow up testing
Half Life vs. Duration

- It is claimed that T4 has a half life of 7 days……then why do we dose it every 24 hours?
  - Levels drop to baseline in most in 18-20 hours
  - Duration of action is approximately 20 hours

- It is claimed that T3 has a half life of 1 to 1.5 days, but is dosed up to 4 times a day
  - Duration of action is 4-6 hours
Interpretation of Testing

- If 24 hours or more have passed since the last dose of TRT, then resulting levels are not correlated to dose but show more of a baseline production from the thyroid gland.
Interpretation of Testing

- For T4, peak occurs 2-4 hours post dose and levels drop off in 18-20 hours.
- For T3 (IR) peak occurs in 1 to 1.5 hours and levels drop off after 4-6 hours.
- For combination T4 and T3 IR products, test at 4 hours after last dose.
- For any compounded SR preparation, best time to test is 4-8 hours after last dose.
Thyroid USP (Desicated Thyroid)

• 1 Grain (60 mg) of Thyroid USP contains only 38 mcg of T4 and 9 mcg of T3
  – More than 99.9% of contents of thyroid USP are not the thyroid hormones T3 and T4

• Ratio of T4:T3 is 4.2:1, which is not physiological
• Ratio is fixed – doesn’t allow for individual differences in metabolism or changes with time
Thyroid USP

• May also contain T2, T1, selenium, calcitonin
  – T2 & T1 may provide biological activity but overall contribution is considered minimal
  – The amounts are not identified, quantified, or standardized

• May contain lactose, sucrose, dextrose, starch or other “suitable” diluents
T4 or T3?

• In nonthyroidal illness or euthyroid sick syndrome:
  – T4 found of little benefit when used in acute conditions (trauma, surgery, sepsis)
    • Diminished use and uptake of T4
  – T3 treatment has been shown significantly beneficial in studies of severely ill patients
    and in chronically ill patients
Thyroid Of Choice

• Liothyronine Sodium used most often
  – “Levothyroxine is the agent of choice, rather than a preparation containing triiodothyronine (T3), since T3 has a short half-life and requires multiple daily doses to maintain blood levels in the normal range”*

Thank You

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