A Functional Approach to Hypothyroidism

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Objectives

• Review the production, metabolism, and activities of the thyroid gland and thyroid hormones
• Differentiate types of clinical hypothyroidism
• Describe the causes, types and symptoms of hypothyroidism
Less Than Optimal Thyroid Function

- A number of situations can contribute
  - Autoimmune reaction involving the thyroid
  - 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
TRH $\rightarrow$ **Pituitary Gland**

TSH $\rightarrow$ **Thyroid Gland**

**Hypothyroidism**

T3 $\rightarrow$ T4
Thyroid Gland

TRH → Pituitary Gland → TSH → Thyroid Gland

T4

T3

fT3

TRH → Pituitary Gland

TSH → Thyroid Gland

T3 → fT3

X

X

X

X

Functional Hypothyroidism
Thyroid Gland

TRH → Pituitary Gland

TSH → +

Thyroid Gland

→ T4

→ T3

Effects On Body (Symptoms)

Functional Hypometabolism

Thyroid receptor in tissue cells

Thyroid Hormone Resistance
Screening

• Screening test refers to simple test that validates that there should be further more involved testing
• Screening itself gives no information to diagnose or treat
• Basal Body Temperature x 3 days
• Ankle Reflex
• TSH
• But the best “screening test” is...
  ...Patient Symptoms
Symptoms of Low Thyroid Function

- Fatigue (especially evening)
- Low stamina
- Cold extremities
- Intolerance to cold
- Headaches, esp. in a.m.
- Myxedema
- Swollen, puffy eyes
- Dry skin
- Brittle nails
- Dry, brittle hair
- Scalp hair loss
- Constipation
- Weight gain
- Depression
- High cholesterol
- Anxiety
- Low pulse rate/blood pressure
- Poor concentration
- Memory lapses
- Heart palpitations
- Low libido
- Infertility
- Fibromyalgia
- General aches and pains
- Slow wound healing
- Loss of outermost portion of eyebrows
Decreased Thyroid Function

- Many of the conditions leading to hypothyroidism involve lifestyle and nutrition
  - Irregular immune function
  - Poor blood sugar metabolism
  - Adrenal issues
  - Gut inflammation/infections
  - Hormone imbalances
- Correcting causes usually takes time and not easy to accomplish
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)
Mild Thyroid Failure

- Non-treatment results in
  - Increased cholesterol levels
  - Significant increased risk of cardiovascular events
    - Endothelial dysfunction with impaired vasodilation
  - Significant increased risk for artherosclerosis and myocardial infarction
    - MTF is a greater risk for MI than hypercholesterolemia, hypertension, smoking or even diabetes
    - MTF may be contributing factor in 60% of myocardial infarctions
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 $\rightarrow$ Pituitary Gland

TSH $\rightarrow$ Thyroid Gland

T4 $\rightarrow$ T3

Hypothyroidism
Causes of Overt Hypothyroidism

- Thyroid function decreases with age
  - Two to three fold increase in hypothyroidism incidence with age
  - Decrease in production occurs at ages 45-50 in normal individuals
Causes of Overt Hypothyroidism

• Lack of components that make up thyroid hormones
  – Iodine
    • Iodine deficiency is the most common cause of hypothyroidism for most of the world’s population per the American Thyroid Association
    • 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
Overt (Primary) Hypothyroidism

- Lack of production: measured best by TT4
- Nutritional support includes iodine, tyrosine, ashwagandha, Vitamin A, Vitamin D, selenium and zinc
- ThRT required if nutritional/lifestyle support does not increase thyroid hormone production and address symptoms
Overt (Primary) Hypothyroidism

- TPO: enzyme responsible for making thyroid hormone
  - Liberates iodine that is added to tyrosine
- Cofactors for this process include pyridoxal-5-phosphate, riboflavin, niacin, magnesium, selenium, zinc and copper
Thyroid Gland

TRH $\rightarrow^+$ Pituitary Gland

TSH $\rightarrow^+$ Thyroid Gland

TSH $\rightarrow$

T4 $\rightarrow$

T3 $\rightarrow$

fT3

Functional Hypothyroidism

X

X

X
Functional Hypothyroidism

• Adequate production of hormone but metabolic pathways impaired (euthyroid)
  – Often can be addressed at least partially with lifestyle adjustments and nutritional support
  – Test results can be within “normal” ranges but patient has symptoms
  – Also could be termed euthyroid
  – Thyroid gland is fine – production is adequate
  – ThRT is not required
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
T4  Thyroxin (Inactive))

5' deiodinase

5 deiodinase

T2  (Active?)

5' deiodinase

rT3  Reverse T3
(Inactive – Binds to T3 receptors)

Normal T4 Conversion to T3 by the Enzyme 5'deiodinase.
T4 Thyroxin (Inactive)

T2 (Active?)

rT3 Reverse T3 (Inactive – Binds to T3 receptors)

5’deiodinase

5 deiodinase

Inhibition of T4 Conversion to T3 by the Enzyme 5’deiodinase.
T4 to T3 Conversion

• Normally, T4 is converted peripherally to almost equal parts T3 and reverse T3
• Decreased conversion to T3 is always accompanied by an increased conversion to reverseT3
• T4 therapy with imbalanced conversion worsens the situation
T4 to T3 Conversion

• The active hormone is T3
  – T4 is an inactive prohormone
  – No T4 receptors have been identified in the body
  – Reported relative strengths determined by s.q. administration and measuring outcomes
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
Metabolism of Thyroid Hormones

- Other pathways:
  - Conjugation with glucuronate or sulfate—secreted in bile
  - Decarboxylation
  - 20-40% of T4 eliminated in the stool
Thyroid Conversion

- 93-94% of the thyroid hormones produced in the thyroid gland is T4
- 80% of T4 produced is peripherally converted to T3.
  - About half is converted to active T3
- About 20% of T4 is converted to T3 sulfate and T3 acetic acid which in the gut in presence of sufficient healthy gut flora can be converted to T3
Thyroid Conversion & Liver Function

• The liver is responsible for much of the conversion of T4 to T3 through conjugation pathways, so a properly functioning liver is essential to healthy thyroid function.

• Hypothyroidism depresses liver function
  – Detoxification enzymes.

• Attempts to improve detoxification and improve thyroid function should be initiated simultaneously.
Improper Conversion of T4 to T3

- High cortisol
- Chronic inflammation or infection
  - Lipid peroxidation causes cell membrane deterioration
- Support includes adrenal support prn, addressing stressors, phosphatidylserine, adaptogens, antioxidant (glutathione, superoxide dismutase, α-Lipoic Acid), selenium, zinc, guggulu
Factors That Inhibit T4 to T3 Conversion

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

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
- Antibiotic use

- Opiates
- Phenytoin
- Chemotherapy
- Theophylline
- Lithium
**Excessive Testosterone**

- Leads to excess free T3
  - Increases conversion of T4 to T3
  - Decreases production of TBG
  - However, recent study indicates excess testosterone interferes with T3 function.
    - Can lead to thyroid hormone cellular resistance
Excessive Testosterone

• Seen with insulin resistance, PCOS, excessive testosterone supplementation/transference

• Support includes
  – Lower the supraphysiologic dose of testosterone!
  – Addressing insulin resistance
  – Liver detox for hormone overload
  – I3C/DIM with proper support for safe estrogen metabolism if excessive estrogen
    • Support conjugation and methylation
Treatment of Poor Conversion

- Address stressors and stress reaction
- Check for heavy metal toxicities
- Liver detoxification
- 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 1000mcg to 2000 mcg daily
- Remove other factors and medications as necessary if possible
- Restore hormone balance at physiologic levels
Thyroid Gland

TRH $\rightarrow^+$

Pituitary Gland

TSH $\rightarrow^+$

Thyroid Gland

$\downarrow$

T4

$\downarrow$

T3

Effects On Body (Symptoms)

Thyroid Hormone Resistance

Thyroid receptor in tissue cells

Functional Hypometabolism
Functional Hypometabolism

- Thyroid not getting absorbed into the cells and transported to the nucleus properly
  - Low cortisol
  - Ferritin less than optimal
  - Elevated homocysteine levels?
    - Inhibits retinoic acid synthesis
- Thyroid receptor less than optimally responsive
  - High or low cortisol
  - Vitamin D level less than 60 ng/dl
  - Low iodine
Vitamin D & Functional Hypometabolism

- Affects thyroid receptor response (Jeffrey Bland, PhD)
- 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
Ferritin & Functional Hypometabolism

- Ferritin is 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
Other Causes of Functional Hypometabolism

- Excessive progesterone, Vitamin D or EFA
- Chronic low cortisol
  - Less transport into cells
  - Less T3 receptors
- High reverse T3 (poor conversion)
  - Blocks T3 at receptor
- High TPO
  - Decreases transport of T3 into cell
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 → Pituitary → Thyroid Gland

Stressors

Reverse T3 → Thyroid Receptor

Active T3
Causes of Functional Hypometabolism

- Excess cortisol
  - Decreases thyroid receptor responsiveness
- Low cortisol
  - Decreases thyroid receptor responsiveness
  - 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
Normal Thyroid Function Requires Normal Adrenal Function

- **Functional Thyroid Deficiency:** Low Cortisol Function
- **Physiological Cortisol Range:** Optimal Thyroid Function
- **Functional Hypometabolism:** Physiological Cortisol Range
- **Tissue Thyroid Resistance:** High Cortisol Resistance
  - Functional Hypometabolism

Low

High
• 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
Causes of Functional Hypometabolism

• Genetic anomalies of thyroid hormone receptors
• Autoimmune (antibodies), oxidative, or toxic damage to thyroid-hormone receptors (heavy metal toxicities)
  – Elevated TH-1 or TH-2 cytokines
• Competitive binding to thyroid-hormone receptors by pollutants, food additives, etc.
  – (halogens, pesticides, perchlorate)
Thanks for Listening!

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