The Terrible "T's" of Thyroid Testing TSH, T4 and T3

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DISCLOSURES

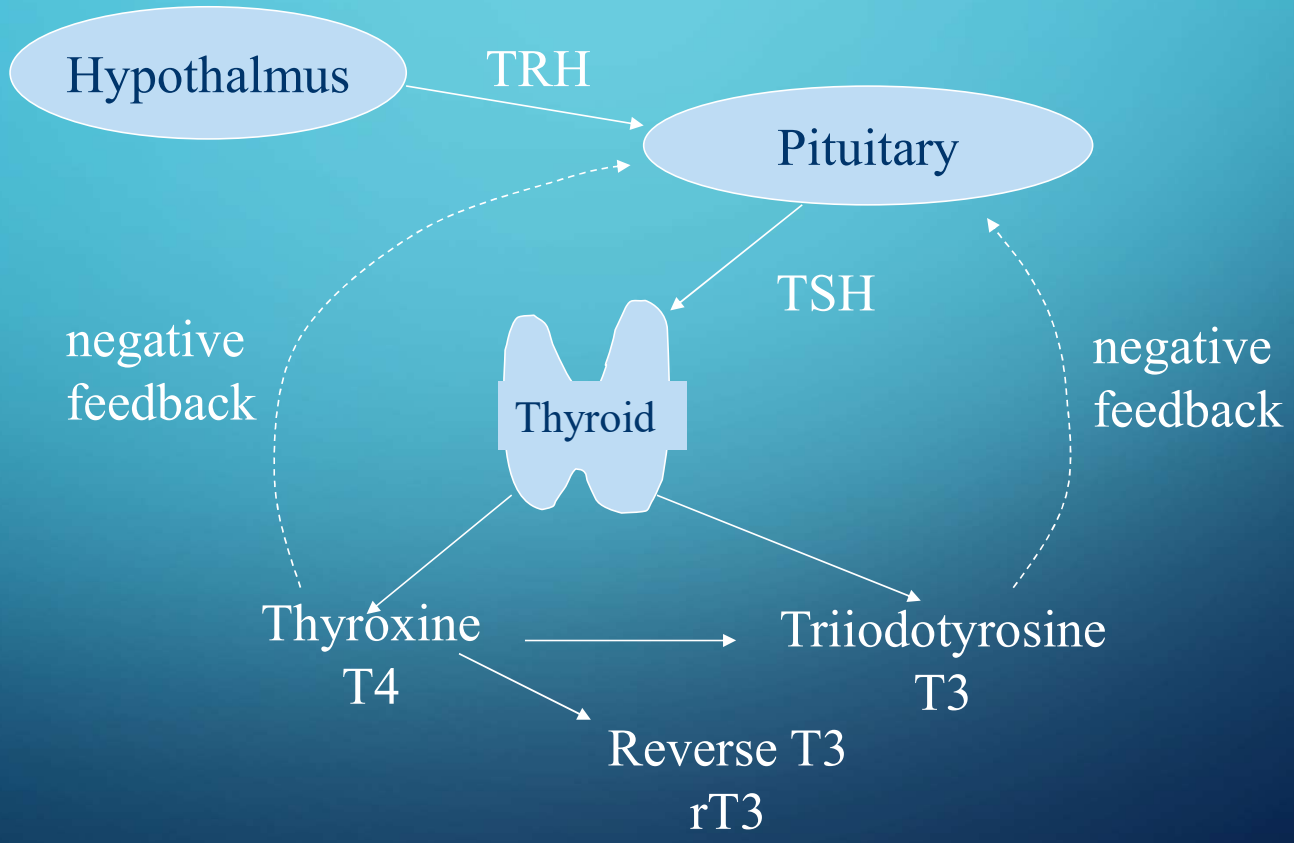
Non-Declaration Statement: We have no relevant relationships with ineligible companies to disclose within the past 24 months. (Note: Ineligible companies are defined as those whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.)

OBJECTIVES

At the conclusion of this session, participants should be able to:

- Analyze the actions of and feedback mechanisms regulating TSH, T4 and T3
- Interpret the signs, symptoms and diagnostic laboratory evaluations associated with thyroid disease
- Evaluate how thyroid function test results are used to monitor and adjust related therapy

HYPOTHALAMIC-PITUITARY-THYROID AXIS



REGULATION OF THYROID HORMONE SECRETION

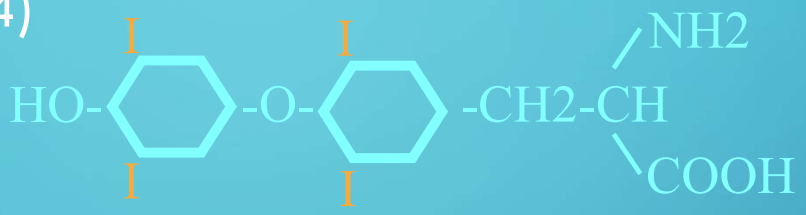
- Thyrotropin-releasing hormone (TRH) is released by hypothalamus
- TRH stimulates the synthesis and release of thyroid stimulating hormone (TSH) from the anterior pituitary gland
- TSH (also called thyrotropin) regulates the release of T4 and T3 from the thyroid gland

THYROID GLAND

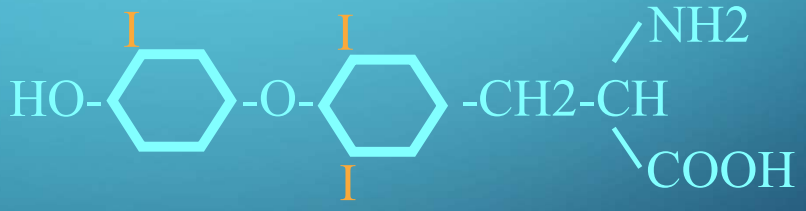
- Synthesizes hormones from tyrosine and iodine (enters through alimentary tract)
- In thyroid gland, iodine incorporated into mono- and di-iodotyrosine which are building blocks for active hormones
  - Thyroxine – T4
  - Triiodothyronine – T3
- Thyroid hormones formed and stored within the thyroglobulin protein molecule in the thyroid gland.

THYROID HORMONES

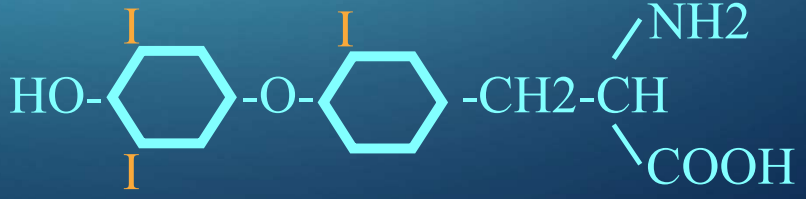
- Thyroxine (T4)



- Triiodothyronine (T3)



- Reverse T3



T4 AND T3

- More T4 than T3 in serum
- T4 converted to T3 by removal of one iodine residue (in peripheral tissues)
- T3 more significant physiologically – exerts majority of thyroidal hormone effects
- T4 half-life = one week
- T3 half-life = one day

THYROID HORMONE CIRCULATION

- Thyroid hormones are bound to thyroid binding globulin (TBG), albumin, or pre-albumin in plasma

- "Free" fraction is physiologically active component
  - Free T4 is 0.02% of total T4
  - Free T3 is 0.20% of total T3

- TBG is increased by estrogen, decreased by androgen

EFFECTS OF THYROID HORMONES

- Control of oxygen consumption – measured by basal metabolic rate
- Affect protein, carbohydrate and lipid metabolism
- Mobilization of electrolytes
- Conversion of carotene to vitamin A
- Development of CNS (mechanism not known)

THYROID TESTS

- Most Common
  - TSH
  - Total T4
  - Free T4
  - T3 Uptake / Free Thyroxine Index*
- Additional testing
  - Labs:
    - Total / Free T3
    - Reverse T3
  - Imaging
    - Radioactive iodine uptake
    - Ultrasound
  - Biopsy
    - Fine Needle Aspirate
  - Serology
    - Autoimmune antibodies

TSH

NORMAL: 0.25-6.7 MILLIUNITS/L

- Most common initial test of thyroid function
  - If level is low or high, additional testing will be needed to determine specific disorder, but normal levels generally indicate normal function of thyroid gland
- Supersensitive, fourth generation assays can measure to 0.004 mU/L

ABNORMAL TSH

- If TSH is high
  - Either thyroid gland is not producing enough T4/T3 OR
  - Pituitary gland is releasing TSH inappropriately OR
  - Very rarely, hypothalamus is releasing TRH inappropriately
- If TSH is low
  - Either thyroid gland is making too much T4/T3 OR
  - Pituitary gland is not making TSH OR
  - Very rarely, hypothalamus is not releasing TRH
- Level of T4 helps differentiate between primary and secondary causes

USE OF TSH IN THERAPY

- Highly sensitive TSH is the most reliable test for adjusting dosage of thyroid replacement therapy in patients with primary hypothyroidism
- Goal of therapy
  - Achieve euthyroid state
  - Lower TSH to mid-normal range
- TSH reflects long-term thyroid status while T4 reflects acute thyroid changes
- Wait 6-8 weeks before rechecking TSH and adjusting dosage

TOTAL T4 (THYROXINE)
NORMAL: 4-12.5 MCG/DL

- Measures both bound and free T4
- Sensitive test for functional status of thyroid gland
  - ↑ in 90% of hyperthyroid patients
  - ↓ in 85% of hypothyroid patients
- Conditions that increase or decrease thyroid-binding protein result in increased or decreased total T4, but do not affect free T4
  - Free T4 level assesses thyroid function more accurately

FREE THYROXINE (FREE T4)

- Two main ways to assess FT4
  1. Free T4 measurement

  2. Free Thyroxine index (FTI)
     - Approximation of free T4 level
     - Calculated value: FTI = T3 Uptake X Total T4
       - T3 uptake test done in lab

FREE T4

NORMAL: 0.8-1.5 NG/DL

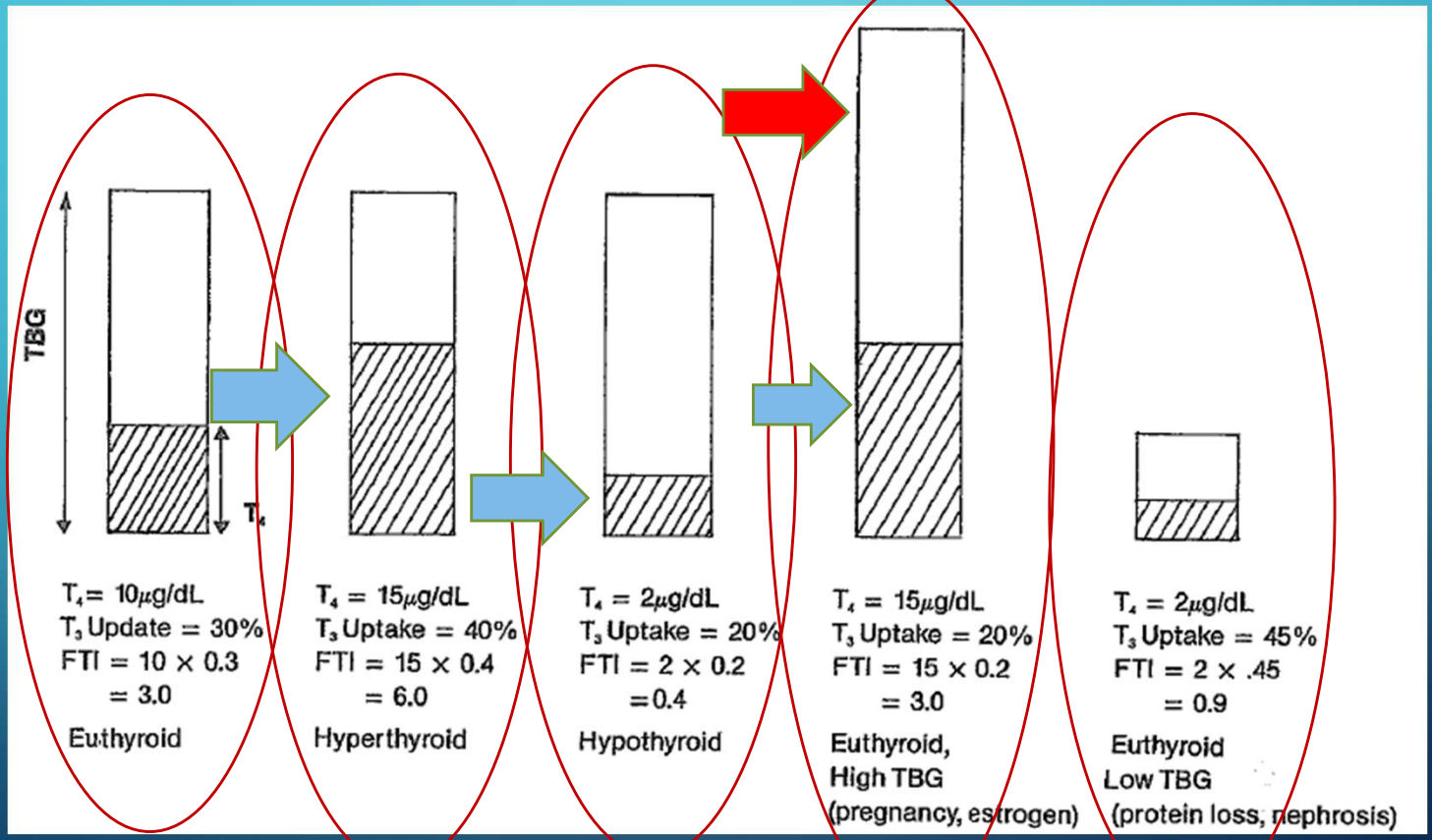
- Measures unbound T4 in serum
- Direct equilibrium dialysis method most accurate
  - ↓ free T4 with ↑ TSH = primary hypothyroidism
  - ↑ free T4 with ↓ TSH = primary hyperthyroidism

FREE THYROXINE INDEX

NORMAL: 1.0-4.0 UNITS OR 0.8-2.7 NG/DL

- Free Thyroxine Index:
  - Equal to Total T4 (mcg/dL) x T3 uptake (%)
- Adjusts for effects of alterations in thyroid-binding protein on total serum T4
- Free Thyroxine Index (equivalent to Free T4):
  - ↑ in hyperthyroidism
  - ↓ in hypothyroidism

T4, T3 UPTAKE AND FTI



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TOTAL T3

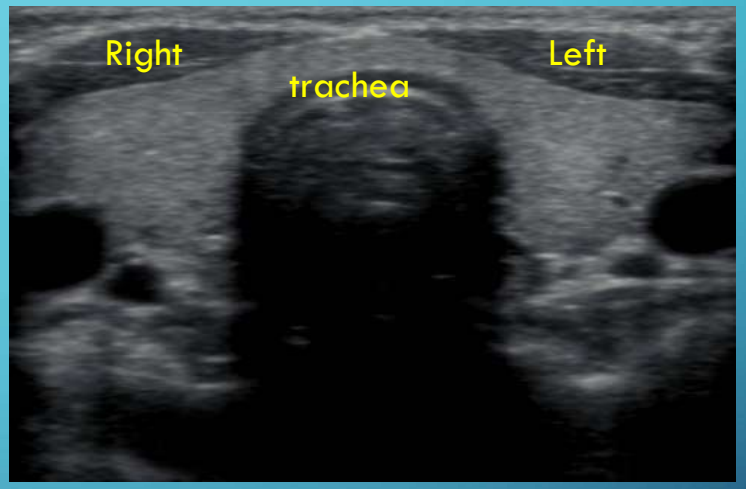
NORMAL: 78-195 NG/DL OR 1.2-3.0 NMOL/L

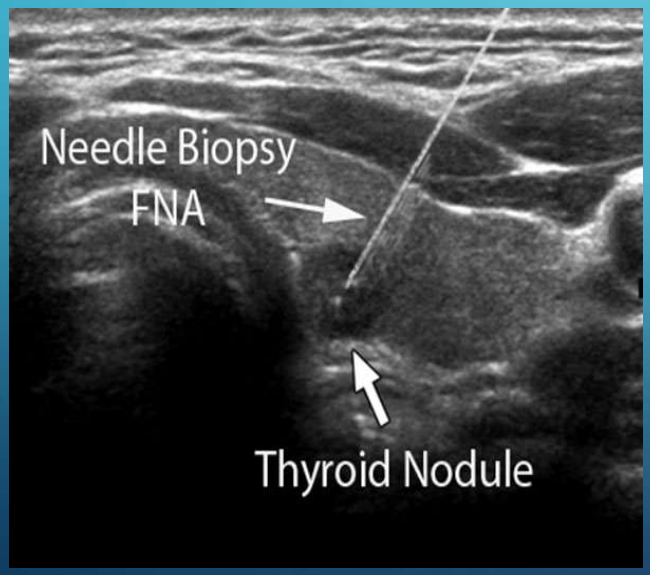
- Total T3 primarily used as an indicator of hyperthyroidism
- Not a reliable indicator of hypothyroidism due to lack of reliability in low to normal range
- Like T4, almost all T3 is protein bound
  - Conditions that increase or decrease thyroid-binding globulin result in increased or decreased total T3, but do not affect metabolically active free T3

ADDITIONAL TESTS

- Free T3:
  - Expensive, not as reliable or as useful (yet)
  - Total T3 measurements more reliable at this time
- Reverse T3:
  - Can help distinguish true thyroid issues in patients with other non-thyroid illnesses in which TSH/T4 are less reliable

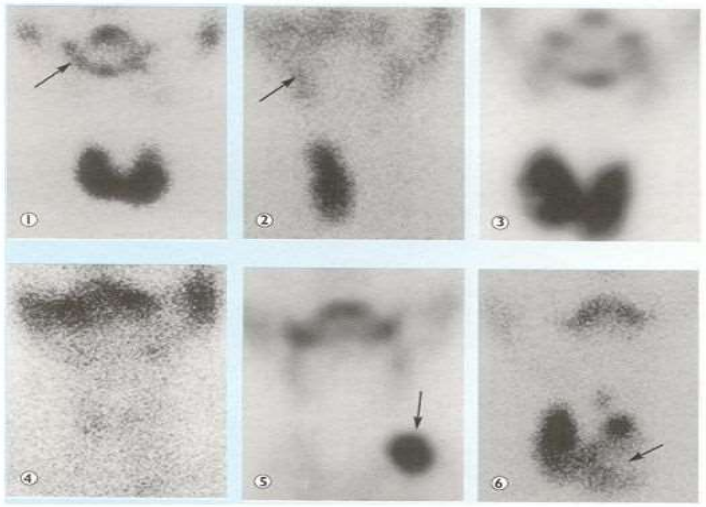
ADDITIONAL TESTS
ULTRASOUND AND FNA





ADDITIONAL TESTS
IMAGING: THYROID UPTAKE SCAN

Thyroid uptake scans



1. Normal thyroid
2. L lobe surgically removed
3. Diffusely increased uptake (e.g. Graves')
4. Decreased uptake (hypothyroidism)
5. Single "hot" nodule with suppression of surrounding tissue
6. "Cold" region in thyroid cancer

SO WHAT DO I ORDER?

- Initial screening – TSH
  - If TSH is high:
    - Free T4 or
    - Total T4/T3 uptake/Free Thyroxine Index
  - If TSH is low: as above, plus Total T3
  - If TSH is normal, but patient has symptoms, consider ordering follow up tests for suspected disorder

BLOOD CHEMISTRY VALUES

- Thyroid hormones affect synthesis, degradation, and intermediate metabolism of adipose tissue and circulating lipids
  - Hyperthyroidism
    - degradation & excretion > synthesis
      - Low levels of cholesterol, phospholipids, triglycerides
  - Hypothyroidism
    - Slows catabolism more than affects synthesis
      - High levels of cholesterol and triglycerides

EFFECTS OF THYROID DYSFUNCTION ON NONTHYROID TESTS

- Hypothyroidism
  - ↑ cholesterol, triglycerides
  - ↑ serum carotene
  - ↑ muscle enzymes
  - ↑ serum prolactin
  - normochromic anemia
  - ↑ capillary fragility
  - ↑ spinal fluid protein
  - ↓ urinary excretion of 17-KS, 17-OHCS (adrenal)
- Hyperthyroidism
  - ↓ cholesterol, triglycerides
  - ↑ aminotransferases and alkaline phosphatase
  - altered glucose insulin relationship
  - ↑ lymphocytes in diff
  - ↑ urinary calcium excretion

THYROID DISORDERS

- Normal functioning thyroid gland = “euthyroid”

- Thyroid disease:
  - 4x more often in women than men
  - Peaks between 3rd and 6th decade
  - Family history often present
  - Primary disorders account for more than 90% of thyroid disorders

HYPOTHYROIDISM

- Results from deficiency of thyroid hormone
  - Body metabolism slows down
- Affects 2% of women; 0.2% of men
  - Incidence increases with age
- Symptoms:
  - Lethargy
  - Constipation
  - Dry, coarse skin and hair
  - Paresthesias /slowed DTRs
  - Facial puffiness
  - Cold intolerance
  - Decreased sweating
  - Impaired memory
  - Slow speech/motor activity
  - Anemia

HYPOTHYROIDISM

- Primary hypothyroidism
  - Failure of thyroid to produce thyroid hormone
  - TSH concentrations > 20 milliunits/L
  - Mild signs/symptoms; TSH values 10-20 milliunits/L
  - Most common cause is chronic autoimmune thyroiditis (Hashimoto's)
- Secondary hypothyroidism
  - Failure of anterior pituitary to secrete TSH
- Tertiary hypothyroidism
  - Failure of hypothalamus to produce TRH

TEST RESULTS - HYPOTHYROIDISM

Disease	TSH		Free T4	OR	FTI	T3	Further workup
Primary Hypothyroidism	↑		↓		↓	**N/A**	**Anti-thyroglobulin or anti-thyroid peroxidase Ab**
Secondary/tertiary Hypothyroidism	↓		↓		↓	**N/A**	**Pituitary MRI**

SUBCLINICAL HYPOTHYROIDISM

Disease	TSH		Free T4	OR	FTI	T3
Subclinical Hypothyroidism	↑		**N**		**N**	**N/A**

Management is still controversial:

- Asymptomatic – treat if TSH >10; monitor
- Symptomatic:
  - Age > 65 – treat if TSH > 6.9
  - Age < 65 – treat

HASHIMOTO'S THYROIDITIS

- Most common cause of hypothyroidism
- Associated with glandular enlargement (goiter)
- ↑ thyroglobulin antibodies
- ↑ thyroid peroxidase (microsomal) antibodies
- Thyroid hormone levels start off normal, then become hypothyroid
  - Normal → low T4

HYPERTHYROIDISM

- Excess amounts of thyroid hormone due to hyperactivity of thyroid gland
- Caused by
  - Overproduction of hormone (Graves disease; goiter) – most common
  - Thyroid destruction (thyroiditis)
  - Drugs
  - Metastatic thyroid cancer
- Signs/symptoms:
  - Nervousness
  - Fatigue
  - Weight loss
  - Heat intolerance
  - Increased sweating
  - Tachycardia or a-fib
  - Muscle atrophy
  - Warm, moist skin
  - Exophthalmos

TEST RESULTS - HYPERTHYROIDISM

Disease	TSH		Free T4	OR	FTI	Total T3	Further workup
Primary Hyperthyroidism	↓		↑/(N)		↑/(N)	↑/(N)	Anti-TSH receptor Ab; thyroid uptake scan or ultrasound
Secondary/tertiary Hyperthyroidism	↑		↑/(N)		↑/(N)	↑/(N)	Pituitary MRI

GRAVES DISEASE

- Most common cause of hyperthyroidism
- Autoimmune antibodies against TSH receptor
  - Stimulates receptor in same manner as TSH – promotes hormone formation

TEST RESULTS IN THYROID DISORDERS

Disease	TSH	Free T4 or FTI	T3
Hashimoto's Thyroiditis *	↑	↓	N/A
Graves Disease**	↓	↑↑	↑

* Presence of thyroglobulin or microsomal antibodies
** Presence of TSH receptor antibodies

MYXEDEMA COMA

- Severe form of hypothyroidism
  - High rate of mortality (25-50%)
- Symptoms
  - Lethargy/Coma
  - Bradycardia
  - Hypothermia
  - Altered mental status
  - Periorbital edema
- Diagnostics
  - Similar to hypothyroidism
    - High TSH, low T4

THYROID STORM

- Severe form of hyperthyroidism
  - High rate of mortality (8-22%)
- Symptoms
  - Fever
  - Tachycardia
  - Altered mental status
- Diagnostics
  - Similar to hyperthyroidism
    - Low TSH, high T4 and T3
    - Similar levels to uncomplicated hyperthyroidism

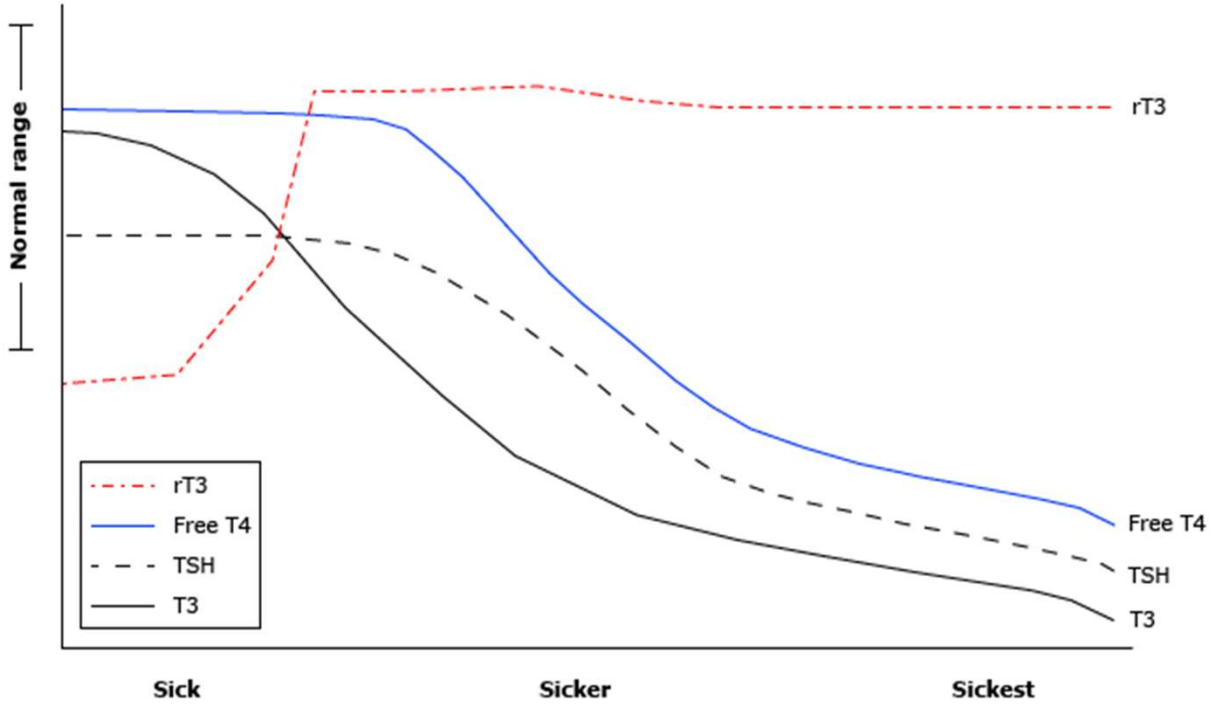
SUBACUTE THYROIDITIS

- Virally induced
- Treatment is symptomatic, with anti-inflammatory meds for pain, and beta blockers if the hyperthyroid symptoms are severe
- Early stage
  - Hyperthyroidism: Elevated T4 and T3; low TSH
- Disease progression
  - Thyroid hormones depleted
  - Hypothyroidism: Low T4 and T3; elevated TSH

EUTHYROID SICK SYNDROME (ETS)

- AKA: Nonthyroidal illness (NTI)
- Severe illness or starvation decreases total T3 and free T3 (decrease in conversion of T4 to T3), increases rT3, no change of free T4 (euthyroid sick syndrome)
- Serum prealbumin drops rapidly
- Low active hormone + low binding capacity = normal FTI
- Normal TSH, T3 level ↓, Reverse T3 level ↑

Thyroid function tests in nonthyroidal illness



Schematic representation of the changes in thyroid function tests in patients with nonthyroidal illness of increasing severity.

rT3: reverse triiodothyronine; T4: thyroxine; TSH: thyroid-stimulating hormone; T3: triiodothyronine

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SCREENING FOR THYROID DISEASE

- Not recommended to screen all patients
- Screening guidelines: conflicting recommendations
  - No recommendations for screening (AAFP; USPSTF)
  - Populations to consider screening, per guidelines
    - Females 50 years of age or older (ACP)
    - All patients with risk factors, including FH (ATA)
    - Any patient $\geq$ 60 years old (ATA)
  - Additional populations to consider screening
    - All adults with newly diagnosed dyslipidemia
    - Younger adults with new onset atrial fibrillation

CASE STUDY

- A 28-year-old female reports for her yearly physical examination complaining of weakness, fatigue, difficulty concentrating on her work, and a noticeable decline in her memory over the past several months. She works as an attorney and attributes many of these symptoms to the severe stress generated by her legal case-load. Further questioning reveals that the frequency of her bowel movements have decreased from once daily, six months ago, to one every two to three days. She is having difficulty avoiding a gain in weight, and despite warm weather, feels chilled without a light sweater. Her only medication is an oral contraceptive.

CASE STUDY (CONTINUED)

- Physical examination reveals a well-proportioned woman, 65 inches, 125 lbs, with pallor and sparse eyebrows (particularly at the lateral margins). Her facial features appear slightly puffy in comparison to the photograph on her driver's license taken three years before. Pulse rate is 50 BPM and blood pressure 110/70. Examination of her neck discloses a mildly enlarged thyroid gland. Her deep tendon reflexes are normally contractive but show a delayed relaxation phase.

CASE STUDY (CONTINUED)

- The initial clinical impression is that of moderate hypothyroidism of several months' duration. Pallor and weakness could also be attributed to anemia.

- The following laboratory results are obtained:

COMPLETE BLOOD COUNT

	Patient Value	Normal Range (female)
WBC	8.0 x 10^9/L	4.4 – 11.3
RBC	4.30 x 10^{12}/L	4.1 – 5.1
Hemoglobin	11.8 g/dL	12.3 – 15.3
Hematocrit	36.1 %	37-47
MCV	83.8 fL	80 - 96
MCH	27.5 pg	27.5 – 33.2
MCHC	32.7 g/dL	33.4 – 35.5
RDW	14.8 %	11.5 – 15.0
PLT	369 x 10^9/L	150 - 450

Monospot Test = negative

CHEMISTRY RESULTS

	Patient Value	Normal Range
Sodium	130 mEq/L	136 - 145
Potassium	3.8 mEq/L	3.5 – 5.0
Chloride	92 mEq/L	96 - 106
CO2	28 mEq/L	24 - 30
Calcium	9.5 mg/dL	8.5 – 10.8
Glucose	80 mg/dL	70 - 100
BUN	20 mg/dL	8 - 20
Creatinine	1.1 mg/dL	0.7 – 1.5
Cholesterol	235 mg/dL	<200

THYROID FUNCTION TESTING

	Patient Value	Normal Range
TSH	55.0 milliunits/L	0.3 - 5.0
Free T4	0.6 ng/dL	0.8-1.5

CASE STUDY (CONTINUED)

- The increased TSH and decreased Free T4 confirms the clinical impression of hypothyroidism.
- The cause of hypothyroidism may be primary (thyroid dysfunction), secondary (pituitary dysfunction), or tertiary (hypothalamic dysfunction). In this case, the elevated TSH with a concordantly low FTI indicates primary hypothyroidism. The etiology of this thyroid dysfunction is likely to be autoimmune thyroiditis (Hashimoto's thyroiditis).
- Anti-thyroglobulin and Anti-thyroid peroxidase antibody titers are obtained.

FURTHER TESTING

	Patient Value	Normal Range
Anti-thyroglobulin Antibodies	Positive 1:640	Negative
Anti-thyroid peroxidase Antibodies	Positive 1:5120	Negative

CASE STUDY (CONTINUED)

- The patient was started on levothyroxine 1.6 mcg/kg/day. Eight weeks later at her follow-up appointment, she complained of “feeling jittery” with palpitations and increased sweating.

- Her TSH was <0.3 milliunits/L. Levothyroxine dosage was reduced, and the patient became asymptomatic after 2 weeks.

LABORATORY TESTING
EIGHT WEEKS AFTER DOSAGE CHANGE

	Patient Value	**Normal Range**
TSH	1.5 milliunits/L	0.3 - 5.0
Free T4	1.2 ng/dL	0.8-1.5
Cholesterol	190 mg/dL	<200
Sodium	138 mEq/L	136 - 145
Hematocrit	40 %	37-47

CASE WRAP-UP

- The highly sensitive TSH is most reliable to monitor and adjust doses of thyroid supplements in patients with hypothyroidism, especially in patients taking oral contraceptives.

- With the newer TSH assays, it is possible to determine excessive suppression of TSH by thyroid replacement medication (<0.004 milliunit/L).

TAKE HOME POINTS

- Diagnostic laboratory evaluation of TSH, T4 and T3, when assessed along with the patient's signs and symptoms, can help differentiate thyroid disease.

- Conditions or medications that increase or decrease thyroid binding protein may cause abnormalities in thyroid function tests, while the patient remains euthyroid.

- Highly sensitive TSH is the most reliable test for diagnosing thyroid disorders and adjusting dosage of thyroid replacement therapy in patients with primary hypothyroidism.

CITATIONS

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