


# Thyroid Essentials: From Hormone Synthesis to Clinical Chemistry Testing

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2026 Clinical Laboratory Collaborative

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## Disclosures

- I have nothing to disclose

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## Learning Objectives

 Diagram and explain the feedback mechanism between the hypothalamus, pituitary, and thyroid gland.

 Describe the synthesis, structure, secretion, and transport of thyroid hormones and precursors.

 Compare commonly used thyroid function tests and justify their appropriate use in clinical scenarios.

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### Function of thyroid hormones

- Stimulates general metabolism
- Energy expenditure
- Heat production
- Involved in growth, maturation and sexual development
- Stimulates protein synthesis and carbohydrate/lipid metabolism
- Increased lipolysis and fatty acid oxidation
- Affects heart rate and heart contraction
- Neurologic development

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### Clinical relevance

Symptom	Primary Hypothyroidism	Secondary Hypothyroidism
Skin changes	Coarse, thick, dry, slightly yellow skin	Pale white, finely wrinkled, transparent skin
Metabolic rate	Decline significantly	Mild reduction
Hair changes	Sparse hair in axilla/pubis possible, but not total loss	Sparse hair in axilla/pubis common, up to total loss
Fatigue, Weight Gain, Cold Intolerance	Common and pronounced	Common and pronounced
Reproductive Symptoms	May have menstrual irregularities, typically not severe	Amenorrhea, testicular atrophy possible
Autoimmune Markers	Commonly present if autoimmune related	Typically absent
Goiter Presence	More common due to chronic TSH stimulation	Less common

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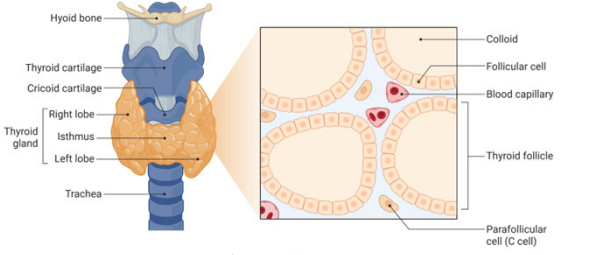
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### Thyroid Gland Anatomy and Histology



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### Biosynthesis of thyroid hormone (1 of 2)

1. Iodide (I<sup>-</sup>) trapping by thyroid follicular cells
2. Diffusion of iodide to the cell and transport into the colloid
3. Oxidation of inorganic iodide to iodine and incorporation into tyrosine residues within thyroglobulin molecules in the colloid

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### Biosynthesis of thyroid hormone (2 of 2)

4. Combination of two diiodotyrosine (DIT) molecules to form tetraiodothyronine (thyroxine, T<sub>4</sub>) or of moniodotyrosine (MIT) with DIT to form triiodothyronine (T<sub>3</sub>)
5. Uptake of thyroglobulin from the colloid into the follicular cell by endocytosis, fusion of the thyroglobulin with a lysosome, and proteolysis with release of T<sub>4</sub> and T<sub>3</sub>
6. Release of T<sub>4</sub> and T<sub>3</sub> into the circulation

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### T<sub>3</sub> and T<sub>4</sub> are the active forms.

Thyroid hormone Thyroxine (T<sub>4</sub>)

CC(=O)O[C@@H](NC)C1=CC=C(C=C1)C2=CC(=C(C=C2)O)C(=O)O

↓ monodeiodinase

Inactive thyroid hormone 3,3',5'-Triiodothyronine (T<sub>3</sub>)

CC(=O)O[C@@H](NC)C1=CC=C(C=C1)C2=CC(=C(C=C2)O)C(=O)O

Active thyroid hormone 3,3',5'-Triiodothyronine (T<sub>3</sub>)

CC(=O)O[C@@H](NC)C1=CC=C(C=C1)C2=CC(=C(C=C2)O)C(=O)O

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### Transport in Plasma

- Immediately bound to proteins
  - Thyroxine-binding globulin (TBG) primary binding
  - Prealbumin
  - Albumin
- >99% bound
- <1% free
  - 0.04% T4 and 0.4% T3 biologically active

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### Tests for Thyroid Function: TSH

- Most useful test for assessing thyroid function is **TSH**.

	Low Free T <sub>4</sub>	Normal Free T <sub>4</sub>	High Free T <sub>4</sub>
Low TSH	Secondary hypothyroidism Severe nonthyroidal illness	Subclinical hyperthyroidism Nonthyroidal illness	Primary hyperthyroidism
Normal TSH	Secondary hypothyroidism Severe nonthyroidal illness	Normal	Test artifact Secondary hyperthyroidism Preanalytic error caused by blood drawn within 6-9 h of thyroxine dose
High TSH	Primary hypothyroidism	Subclinical hypothyroidism	Test artifact Secondary hyperthyroidism Thyroid hormone resistance <sup>a</sup>

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### Tests for Thyroid Function: FT4

- Free Thyroxine (FT4)
  - Small fraction of total thyroxine (0.04%)
  - Most bound to thyroid carrier proteins
  - FT4 is available to enter the tissues
  - Biologically active fraction
  - Reflex in TSH w/reflex
    - If TSH abnormal, FT4 is automatically run as part of order

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**Tests for Thyroid Function: T3 (rare)**

- Triiodothyronine (T3)
  - 20% produced in thyroid
  - Majority peripheral conversion of T4 to T3
  - **More biologically active** than T4
  - Usually ordered when
    - Clinical suspicion of hyperthyroidism
    - Normal/low TSH and free T4 values

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**Tests for Thyroid Function: FT3 (rare)**

- Free Triiodothyronine (FT3)
  - Suspicion is disturbance of binding proteins
  - More FT3 than a T3 level indicates
    - Pregnancy
    - Dysalbuminemia

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**Tests for Thyroid Function: Autoantibodies**

- Thyroglobulin Antibody (Tg)
- Thyroperoxidase Antibody (TPO)
- Thyrotropin Receptor Antibody (TRAb)

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**Autoantibodies: Thyroglobulin Antibody (Tg)**

- **Thyroglobulin Antibody (Tg)**
  - Leakage of Tg into the bloodstream
  - Formation of Tg antibodies
  - Graves' disease: 12% to 30% of patients
  - Hashimoto's Thyroiditis: 35% to 60% of patients

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**Autoantibodies: Thyroperoxidase Antibody (TPO)**

- **Thyroperoxidase Antibody (TPO)**
  - Activate complement
  - Play an important role in pathogenesis of hypothyroidism
  - Graves' disease: 45% to 80% of patients
  - Hashimoto's Thyroiditis: 80% to 99% of patients

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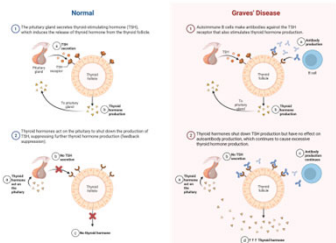
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**Autoantibodies: Thyrotropin Receptor Antibody (TRAb)**

- **Thyrotropin Receptor Antibody (TRAb)**
  - Can be blocking or stimulating antibodies
  - Graves' disease is caused by the production of stimulating TRAb



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**Strengths & Limitations: TSH**

- Strengths
  - Best **initial test** for thyroid function
  - Very **sensitive to small changes** in thyroid hormone levels
  - Helps distinguish **primary** vs. **secondary** disorders
  - Stable and reliable across most clinical conditions
- Limitations
  - May appear **normal in pituitary/hypothalamic** disease (secondary/tertiary hypothyroidism)
  - Can be affected by **severe illness**
  - Slow to adjust to therapy

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**Strengths & Limitations: FT4**

- Strengths
  - Helpful when TSH abnormal
  - Not affected by changes in binding proteins
- Limitations
  - Assays vary between laboratories
  - Altered results in severe illness and pregnancy

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**Strengths & Limitations: Total T4**

- Strengths
  - Often reliable in stable patients
- Limitations
  - Strongly affected by binding protein changes (pregnancy, estrogen therapy, liver disease)
  - Can be misleading without FT4

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**Strengths & Limitations: FT3**

- Strengths
  - Useful when **T3 toxicosis** suspected
  - Helpful when **binding protein abnormalities** make total T3 unreliable
- Limitations
  - Limited diagnostic value for hypothyroidism
  - Assays less standardized

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**Strengths & Limitations: Total T3**

- Strengths
  - Helpful in diagnosing **T3 hyperthyroidism**
- Limitations
  - Less useful in hypothyroidism
  - Decreased in situations of chronic illness

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**Strengths & Limitations: Autoantibodies**

- Strengths
  - Help diagnose autoimmune thyroid disease
  - TPO: highly sensitive for Hashimoto's
  - Tg antibody: autoimmune disease
  - TRAb: Confirms Grave's disease
- Limitations
  - Presence of antibodies doesn't always correlate with severity
  - Some antibodies can be present in healthy individuals
  - Only TRAb useful to monitor treatment

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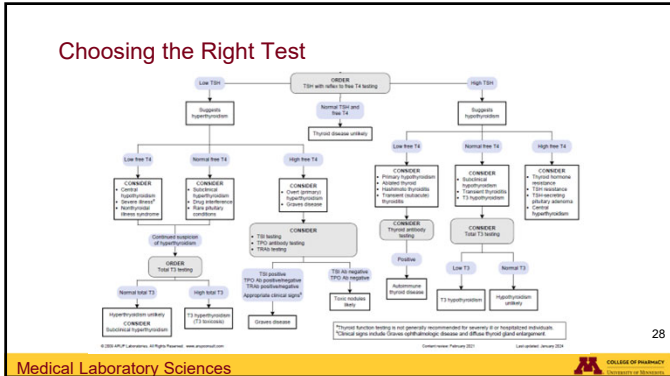
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- ### Key Takeaways
- TSH is the best initial test
  - FT4 clarifies abnormal TSH
  - Total T4 and T3 are influenced by binding proteins
  - FT3 has limited routine use
  - Autoantibodies guide diagnosis of autoimmune thyroid disease
  - Interpretation requires context
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### Thank you!

- Happy to answer questions.

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