The Thyroid

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Large Group Session

1. Thyroid Anatomy, Embryology, Histology
2. Thyroid Hormone Production, Regulation, and Actions
3. INXS thyroid hormones (Thyrotoxicosis)
4. Underactive thyroid (Hypothyroidism)
5. Euthyroid thyroid hormone abnormalities
6. Thyroid Structure & Nodules
Thyroid Anatomy

• Weight 10-20 grams
• 2 lobes connected by an “Isthmus”
• Isthmus right below Cricoid cartilage
• Each lobe:
  • Pear shaped
  • 2.5-4.0cm long, 1.5-2.0cm wide, 1.0-1.5cm thick
Embryological Origin

- Thyroid originates as an outpouching in the floor of the pharynx
- Grows downward anterior to the trachea
- Remnants:
  - Thyroglossal duct
  - Pyramidal lobe of thyroid
- Improper descent → Thyroid Ectopia
  - 90% lingual
  - 1/3 under-functioning thyroid gland (hypothyroidism)
Thyroid Anatomy

• Nearby important structures:
  • Internal jugular vein, Carotid arteries
  • Parathyroid glands → Calcium homeostasis
  • Recurrent laryngeal nerves → Voice
Thyroid Histology

• Thyroid is made up of follicles of various size.
• Each follicle is comprised of a single layer of follicular cells surrounding colloid
• Follicular cells synthesize and secrete thyroglobulin into the follicular lumen
Thyroid Function

• Parafollicular cells:
  • Secrete Calcitonin (minor player in Calcium metabolism)

• Essential role of the thyroid is to make thyroid hormones (T4 and T3)

• Thyroid hormone synthesis is carried out at the follicular cell-colloid interface
**Thyroid hormone biosynthesis** Thyroid hormone synthesis includes the following steps: (1) iodide (I⁻) trapping by the thyroid follicular cells; (2) diffusion of iodide to the apex of the cells; (3) transport of iodide into the colloid; (4) oxidation of inorganic iodide to iodine and incorporation of iodine into tyrosine residues within thyroglobulin molecules in the colloid; (5) combination of two diiodotyrosine (DIT) molecules to form tetraiodothyronine (thyroxine, T4) or of monoiodotyrosine (MIT) with DIT to form triiodothyronine (T3); (6) uptake of thyroglobulin from the colloid into the follicular cell by endocytosis, fusion of the thyroglobulin with a lysosome, and proteolysis and release of T4, T3, DIT, and MIT; (7) release of T4 and T3 into the circulation; and (8) deiodination of DIT and MIT to yield tyrosine. T3 is also formed from monodeiodination of T4 in the thyroid and in peripheral tissues. (Modified from Scientific American Medicine, Scientific American, New York, 1995.)
→ T4 → Protein* binding + 0.03% free T4

80% (peripheral)

→ T3 → Protein* binding + 0.3% free T3

(10-20x less than T4)

\[
\begin{align*}
\text{Total T4} & \quad 60-155 \text{ nM} \\
\text{Total T3} & \quad 0.7-2.1 \text{ nM} \\
T_3RU/THBI & \quad 0.77-1.23
\end{align*}
\]

* TBG 75%
TBPA 15%
Albumin 10%
A  Thyroid hormone responsive gene

Transcription → mRNA

Thyroid hormone response element

B  Recognition of thyroid hormone responsive genes
(TR binding to TRE, stabilization by TRAP and transcription silencing by CoR)

TR-TRP
TR-TRP heterodimer

C  Activation of thyroid hormone receptor
(formation of a TR-T3 complex resulting in dissociation of the CoR and recruitment of CoA)
**Pathways of thyroid hormone metabolism**

Thyrotropin-releasing hormone (TRH) increases the secretion of thyrotropin (TSH), which stimulates the synthesis and secretion of triiodothyronine (T3) and thyroxine (T4) by the thyroid gland. T3 and T4 inhibit the secretion of TSH, both directly and indirectly by suppressing the release of TRH. T4 is converted to T3 in the liver and many other tissues by the action of T4 monodeiodinases. Some of the T4 and T3 is conjugated with glucuronide and sulfate in the liver, excreted in the bile, and partially hydrolyzed in the intestine. Some of the T4 and T3 formed in the intestine may be reabsorbed.

+ = stimulatory pathway; - = inhibitory pathway. Drug interactions can occur at any of these sites. (Reprinted with permission from Surks, MI, Sievert, R, N Engl J Med 1995; 333:1688. Copyright 1995 Massachusetts Medical Society. All rights reserved).
TRH stimulates TSH release
TSH stimulates thyroid release
Thyroid inhibits TSH release

Autoimmune disease
TSH receptor-like antibodies stimulate thyroid release
Massive inhibition of TSH release

Pituitary problem
Low TSH release, therefore low thyroid release

Hypothalamic problem
Low TSH and thyroid release
Thyroid Function: blood tests

- TSH 0.4 – 5.0 mU/L
- Free T4 (thyroxine) 9.1 – 23.8 pM
- Free T3 (triiodothyronine) 2.23-5.3 pM
TSH Assay
(0.4-5 mU/L)

- Early RIA < 1.0 mU/L
  - Thyrotoxicosis / 2° hypothyroidism
    - Unable to detect lower range of normal
- Monoclonal SEN < 0.1 mU/L
- Super SEN < 0.01 mU/L
TRH Stimulation test

A) 1° Hypothyroidism
B) Central Hypothyroidism
C) Euthyroid
D) 1° Thyrotoxicosis
TSH

- High
  - FT4
    - High: 1° Hypothyroid
    - Low: 2° thyrotoxicosis
      - Endo consult
      - FT3, rT3
      - MRI, α-SU
  - Low: FT4 & FT3
    - Low: Central Hypothyroid
    - TRH Stim.
    - MRI, etc.
    - If equivocal
      - Endo consult
      - FT3, rT3
      - MRI, α-SU
    - High: 1° Thyrotoxicosis
      - RAIU

- Low
Thyrotoxicosis

• Elevated thyroid hormone levels
• Primary versus Central
  • TSH
• Hyperthyroidism & non-Hyperthyroidism
  • RAIU
RAIU

- Oral dose of I$^{131}$ 5 uCi (or I$^{123}$ 200 uCi but more $)
- Measure neck counts @ 24h (+/- 4h if suspect high turnover)
- RAIU = \frac{\text{neck counts} - \text{bkgd (thigh counts)}}{\text{pill counts} - \text{bkgd}} \times 100

Figure 7–8. Typical curves of 24-hour radiiodine uptake in normal subjects and in patients with thyroid disease.
**RAIU**

- Normal 4h RAIU = 5-15 %
- **24h RAIU:**
  - >25%       Hyperthyroid
  - 20-25%    Equivocal (check TSH)
  - 9-20%     Normal
  - 5-9%      Equivocal (check TSH)
  - <5%       Hypothyroid

- Dependent on dietary iodine intake!
- Must be: not pregnant! (β-hCG), no ATD x 7d, no LT4 x 4d, no large doses of iodine or radiocontrast for 2 wk (prefer 4-6 wk)
**Hyperthyroidism with a high radioiodine uptake**

- Autoimmune thyroid disease
  - Graves' disease
  - Hashitoxiosis

- Autonomous thyroid tissue (uptake may be low if recent iodine load led to iodine-induced hyperthyroidism)
  - Toxic adenoma
  - Toxic multinodular goiter

- TSH-mediated hyperthyroidism
  - TSH-producing pituitary adenoma
  - Non-neoplastic TSH-mediated hyperthyroidism

- Human chorionic gonadotropin-mediated hyperthyroidism
  - Hyperemesis gravidarum
  - Trophoblastic disease

**Hyperthyroidism with a low radioiodine uptake**

- Subacute thyroiditis
  - Subacute granulomatous (de Quervain's) thyroiditis
  - Subacute lymphocytic thyroiditis (painless, silent)
    - Postpartum thyroiditis
  - Amiodarone (also may cause iodine-induced hyperthyroidism)
  - Radiation thyroiditis
  - Palpation thyroiditis

- Exogenous thyroid hormone intake
  - Excessive replacement therapy
  - Intentional suppressive therapy
  - Factitious hyperthyroidism

- Ectopic hyperthyroidism
  - Struma ovarii
  - Metastatic follicular thyroid cancer

**Causes of hyperthyroidism**  Major causes of hyperthyroidism according to the presence of a high or low radioiodine uptake. High uptake indicates increased new hormone synthesis by the thyroid whereas low uptake indicates release of preformed hormone, exogenous ingestion, or extrathyroidal hormone synthesis.
Thyrotoxic S&S

- Heat intolerance
- Weight loss (normal to increased appetite)
- Hyperdefecation
- Tremor, Palpitations
- Diaphoresis
- Lid retraction & Lid Lag
- Decreased menstrual flow
Graves’ Disease

- Most common cause of thyrotoxicosis
- TSH-R antibody (stim)
- Goitre, Orbitopathy, Dermopathy
Subacute (de Quervain’s) Thyroiditis

- Antecedent viral etiology
- Granulomatous infiltration of the gland
- Painful goitre
- Thyrotoxic phase $\rightarrow$ Hypothyroid phase
**Characteristic course of subacute thyroiditis** The initial thyroid inflammation damages thyroid follicles and activates proteolysis of the thyroglobulin stored within the follicles. The result is unregulated release of large amounts of thyroxine (T4) and triiodothyronine (T3) into the circulation and therefore hyperthyroidism. This state lasts only until the stores of thyroglobulin are exhausted, because new hormone synthesis ceases. As the inflammation subsides, the thyroid follicles regenerate and thyroid hormone synthesis and secretion resume. There may be a transient period of hypothyroidism and increased TSH secretion before thyroid secretion becomes normal again. However, some patients have only a hyperthyroid or hypothyroid phase.
Thyrotoxicosis Treatment

• Beta-blockers (hyperadrenergic symptoms)

• Hyperthyroidism:
  • Anti-thyroid Drugs
    – Propylthiouracil (PTU), Methimazole
  • Radioiodine Ablation
  • Surgical Thyroidectomy

• Thyroiditis:
  • ASA, NSAIDS, +/- corticosteroids

• Iodine (high doses ➔ Wolff Chaikoff effect)
Hypothyroidism

• Decreased thyroid hormone levels
• Primary versus Central
  • TSH
  • TRH stimulation
TSH

High
- FT4
  - High: 1° Hypothyroid
  - Low: 2° thyrotoxicosis
    - Endo consult
    - FT3, rT3
    - MRI, α-SU
  - Low: If equivocal
    - TRH Stim.
      - MRI, etc.

Low
- FT4 & FT3
  - Low: Central Hypothyroid
  - High: 1° Thyrotoxicosis
    - RAIU
Major Causes of Hypothyroidism

**Primary hypothyroidism**
- Chronic autoimmune thyroiditis
- Iatrogenic
  - Thyroidectomy
  - Radioiodine therapy or external irradiation
- Iodine deficiency or excess
- Drugs — thionamides, lithium, amiodarone, interferon-alfa, interleukin-2, perchlorate
- Infiltrative diseases — fibrous thyroiditis, hemochromatosis, sarcoidosis

**Transient hypothyroidism**
- Subacute lymphocytic (painless) thyroiditis
- Subacute granulomatous thyroiditis
- Postpartum thyroiditis
- Subtotal thyroidectomy
- Following radioiodine therapy for Graves’ hyperthyroidism
- Following withdrawal of suppressive doses of thyroid hormone in euthyroid patients
- Congenital thyroid agenesis, dysgenesis, or defects in hormone synthesis

**Central hypothyroidism**
- TSH deficiency
- TRH deficiency

**Generalized thyroid hormone resistance**
Hypothyroid S&S

- Cold intolerance
- Weight gain
- Constipation
- Hair loss (telogen effluvium)
- Dry puffy skin
- Hung-up reflexes
- Increased menstrual flow
Hashimoto’s Disease

• Most common cause of hypothyroidism in North America (iodinated salt)
• Autoimmune lymphocytic thyroiditis
• Antithyroid antibodies:
  • Thyroglobulin Ab
  • Microsomal Ab
  • TSH-R Ab (block)

• **Treatment:** Thyroid hormone replacement
Autoimmune Thyroid Disease

TSH-R ab block
Thyroglobulin ab
Microsomal ab

Hashimoto’s

Autoimmune Thyroid Disease

TSH-R ab stim

Grave’s Dx
Thyroid Antibodies

• **Hashimoto’s**
  - Thyroglobulin AB (<40 KIU/L)
  - Thyroid peroxidase AB (< 35 KIU/L)

• **Grave’s**
  - TSI or TSH Receptor Ab (Stim): IgG antibody
  - SEN 60%  SPEC 90%
  - 2-3 month turn-around time
  - Indications:
    » Pregnant & present or past hx Grave’s: check 2nd trimester
      (if hi-titre > 5X normal needs PTU as TSI crosses placenta)
    » ? Euthyroid Grave’s ophthalmopathy
    » Alternating hyper/hypo function due to alternating
      Stim/Block TSI
Euthyroid Hyperthyroxinemia

\[ \text{T4} \rightarrow \text{Protein* binding} + 0.03\% \text{ free T4} \]
\[ \downarrow 80\% \text{ (peripheral)} \]
\[ \text{T3} \rightarrow \text{Protein* binding} + 0.3\% \text{ free T3} \]
\[ \downarrow 20\% \]
\[ (10-20x \text{ less than T4}) \]

Total thyroid hormones affected by binding protein levels!

\[
\begin{align*}
\text{Total T4} & \quad 60-155 \text{ nM} \\
\text{Total T3} & \quad 0.7-2.1 \text{ nM} \\
\text{T}_3\text{RU/THBI} & \quad 0.77-1.23
\end{align*}
\]

* TBG 75%  
* TBPA 15%  
* Albumin 10%
**T₃RU (T3 Resin Uptake)**

1. **T³* (radio-labeled)**
   - Patient’s serum
   
2. Incubate
   - Insoluble resin (traps unbound T³)
   
3. **T³*-TBG
   - T³*
   - T³*-TBG

4. Measure % tracer bound to resin

```
T³* (radio-labeled) → Patient’s serum → Incubate → Insoluble resin (traps unbound T³) → T³*-TBG → T³* → T³*-TBG
```
• Measured the % of T3* tracer bound to resin
• Inversely proportional to # T3 binding sites in patient’s serum.
• # Binding sites dependent on:
  • Binding protein (TBG, TBPA, albumin) levels
  • Endogenous T3 production
• Increased T₃RU:  thyrotoxicosis  or ↓ Binding proteins
• Decreased T₃RU:  hypothyroidism  or ↑ Binding proteins
T₃RU (T3 Resin Uptake)

- Thyroid hormone binding Index (THBI)
- Normalized T₃RU
- \[ \text{THBI} = \frac{\text{patient’s T₃RU}}{\text{mean T₃RU in pool of normal subjects}} \]
- Normal THBI = 1.0 (range 0.77-1.23)
Free Thyroxine Index (FTI)

- Free Thyroxine Index approximates Free T4
- FTI = Total T4 x THBI
- Normal range and units for FTI same as for lab’s Total T4
- **Note:** if FTI calculated using patient’s T₃RU then the result is a unitless number with a normal range distinct for the lab.
## T₃RU (T3 Resin Uptake)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Total T4</th>
<th>T₃RU</th>
<th>FTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyrotoxicosis</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Increased TBG</td>
<td>↑</td>
<td>↓</td>
<td>Normal</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Decreased TBG</td>
<td>↓</td>
<td>↑</td>
<td>Normal</td>
</tr>
</tbody>
</table>
Euthyroid Hyperthyroxinemia

- **Increased TBG**
  - Hereditary (X-linked dominant)
  - Estrogen (pregnant, OCP, HRT, ovarian tumor, tamoxifen, raloxifene)
  - Hepatitis, Acute Intermittent Porphyria
  - Drugs: 5-FU, perphenazine, clofibrate, heroin, methadone

- **Familial dysalbuminemic hyperthyroxinemia (FDH)**
  - Autosomal Dominant, 0.2% Hispanics
  - Mutant albumin binds T4 but not T3
  - Thus total T4 is elevated but T3RU is normal resulting in falsely elevated FTI
  - Prior to sensitive TSH assay these patients often misdiagnosed as hyperthyroid and treated unnecessarily
  - Using radiolabelled T4 instead of T3 allows determination of correct FTI
  - Also can confirm diagnosis by electrophoresis of binding proteins and/or studying family members.

- **Abnormal Transthyretin/Thyroxine Binding Prealbumin**
  - Abnormal TBPA binds T4 but not T3 like FDH
**T3-resin test in familial dysalbuminemic hyperthyroxinemia**

The radiolabeled T3 (\(^*\)T3) binds normally to available binding sites on TBG, but cannot bind to available sites on the abnormal albumin; as a result, the amount left over to bind to the resin is normal. The serum total T4 is high due to excess binding to the abnormal albumin, the T3-resin uptake and THBR are normal, and the serum free T4 index is high.
Euthyroid Hypothyroxinemia

- **Decreased TBG**
  - Hereditary (X-linked recessive)
  - Androgen excess, Cushing’s, Acromegaly
  - Starvation
  - Nephrotic syndrome (urinary loss of TBG)
  - Drugs: L-asparaginase, danazol, niacin

- **Displaced binding to TBG**
  - Salicylates, Lasix (hi doses), some NSAIDS (fenclofenac, mefenamic acid)
  - Heparin (displaces binding to albumin)
Thyroid Structure

- Physical Exam
- Thyroid Ultrasound
- Thyroid Scan
Physical Exam: Goitre
(JAMA, 273:813, 1995)

Inspection & Palpation

Estimated Thyroid Size

Normal
(<20gm)

Still not visible when neck hyperextended

No goitre
(LR+ 0.15)

1-2X normal
(20-40 gm)

Lateral prominence > 2mm?

No

Inconclusive

Yes

No goitre
(LR+∞)

> 2X normal
(> 40 gm)

(LR+ 25)

Goitre ruled in

Thyroid U/S
Thyroid nodules

- U/S more sensitive than P.E., particularly for nodules that are < 1 cm or located posteriorly in the gland.
- U/S also more SEN than thyroid scan
- U/S too Sensitive?
  - Thyroid Incidentaloma (Carotid duplex, etc.)
# Thyroid U/S

<table>
<thead>
<tr>
<th>Benign Characteristics</th>
<th>Malignant Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular border</td>
<td>Irregular border</td>
</tr>
<tr>
<td>Hyperechoic (cystic)</td>
<td>Hypoechoic (solid)</td>
</tr>
<tr>
<td>Egg shell calcification</td>
<td>Microcalcification</td>
</tr>
<tr>
<td>N/A</td>
<td>Intranodular vascular spots (color doppler)</td>
</tr>
</tbody>
</table>

Thyroid Scan

- Technetium-99m Pertechnetate 5-10 mCi IV
- Scan 20 minutes later
- I$^{123}$ 100-400 uCi po, scan 4-6h later ($$)$
Thyroid nodule: risk of malignancy 6.5%

Cold nodule
16-20% malignant

“Warm” Nodule
(indeterminant)
5% malignant

Hot Nodule
Tc-99m < 5% malignant
I\textsuperscript{123} < 1% malignant

only 5-10% of nodules
Fine Needle Aspiration (FNA)

- 25G Needle, 10cc syringe
- Done in Office
- +/- Local
- 3-5 passes
- SEN 95-99% (False Negative rate 1-5%)
- SPEC > 95%
FNA Results

• **Nondiagnostic:** repeat FNA
• **Benign:** macrofollicular or "colloid" adenomas, chronic autoimmune (Hashimoto's) thyroiditis
• **Suspicious or Indeterminant:** microfollicular or cellular adenomas (follicular neoplasm)
• **Malignant**
Benign Lesions

**Macrofollicular lesion**  Low-power view of a fine needle aspirate of a thyroid nodule showing an intact macrofollicle (a) and a macrofollicle that has been broken apart by the biopsy forming a flat sheet (b). At this power, the cells appear uniform in size and are not crowded. Not shown, but commonly present in macrofollicular lesions, are areas of cystic degeneration, cellular debris, and hemosiderin-laden macrophages.

**Hashimoto’s thyroiditis**  Fine needle aspirate of the thyroid in Hashimoto’s thyroiditis. Lymphocytes are predominant, sometimes surrounding rare follicular cells. No formed follicles are seen. Some colloid is present in the background.
Papillary Carcinoma

Surgical Specimen

Papillary carcinoma  Surgical specimen showing the classic histologic appearance of papillary cancer with papillary structure and no follicles or colloid. Follicular development can be seen in some of these carcinomas (follicular variant of papillary cancer); in them, the diagnosis is made from the cytologic features of the cells.

FNA

Papillary thyroid carcinoma  Fine needle aspirate of a thyroid nodule showing papillary carcinoma. The cells and nuclei are large, and their cytoplasm has a “ground glass” appearance. Nucleoli are prominent and the nuclei have clefts, grooves, and “holes” due to intranuclear cytoplasmic inclusions (“Orphan Annie eyes”).
Follicular Lesions on FNA: Can’t Distinguish!

**Microfollicular adenoma** Fine needle aspirate of a thyroid nodule showing microfollicles, with little or no colloid in the background. There is no clumping or pleomorphism. Nevertheless, surgical excision was advised because of the microfollicular pattern. The nodule was benign.

**Follicular carcinoma** Fine needle aspirate of a thyroid nodule showing microfollicles and minimal follicle development. The specimen is cellular, and the cells are crowded, pleomorphic, and clumped. Colloid is scant. This lesion was excised and found to be an invasive follicular cancer.
Incidentaloma
(< 1.0 cm)
Hx of XRT exposure?
Malign U/S risk factors?
FHx of thyroid cancer?

No → Follow U/S q1y

Yes → TSH
- Low
  - Follow U/S q1y
- Normal or High
  - Scan
    - Hot
      - Rx Plummer’s
        - Surgery
        - RAI
    - Not Hot
      - FNA
        - Malignant
          - Total Thyroidectomy
        - Suspicious (Follicular)
          - Hemithyroidectomy with quick section
        - Insufficient Sample
          - Repeat FNA +/- U/S guide
          - Clin suspicion
            - Low
            - High

Follow U/S q1y

Benign → Clin suspicion Low

Malignant (Follicular) → Clin suspicion High