THE THYROID GLAND
AN ALN PRESENTATION

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Learning objectives

- Recognize the location, cell types, and size of the thyroid gland
- List hormones and functions produced by the thyroid gland
- Recognize mechanisms of thyroid hormone production
- Recognize assays used to diagnose thyroid disorders
- Evaluate data to determine which thyroid disease is most likely
THE THYROID GLAND

Embryology
Anatomy
Histology
Physiology
Thyroid Function Tests
& Pathology
Embryology and development

- First endocrine gland to appear in embryonic development
- Begins to develop ~24 days in the thyroid diverticulum
- Descends into the neck and passes anteriorly to hyoid and laryngeal cartilages
- For a time is connected to tongue by thyroglossal duct
- Assumes definitive shape and final location by 7 weeks gestation, and the thyroglossal duct disappears
- Initially consists of solid mass of endodermal cells, which are broken up into network of epithelial cords by invasion of surrounding vascular mesenchyme → lumen forms → colloid forms by 11th week and thyroid follicles are formed, and synthesis of hormones commences
Anatomy

- Single, bi-lobed gland in the neck
- Largest of all endocrine glands
- Produces hormones
  - thyroxine ($T_4$) and tri-iodothyronine ($T_3$) are dependent on iodine and regulate basal metabolic rate
  - calcitonin which has a role in regulating blood calcium levels
- Unique among human endocrine glands – it stores large amount of inactive hormone within extracellular follicles
Anatomy

- Brown-red and soft
- Usually weighs about 25-30g (larger in women)
- Surrounded by a thin, fibrous capsule of connective tissue
  - External to this is a “false capsule” formed by pretracheal fascia
- Right and left lobes
  - United by a narrow isthmus, which extends across the trachea anterior to second and third tracheal cartilages
- In some people a third “pyramidal lobe” exists, ascending from the isthmus towards hyoid bone
Anatomy

- Clasps anterior and lateral surface of **pharynx, larynx, oesophagus and trachea** “like a shield”
- Lies deep to **sternothyroid** and **sternohyoid** muscles
- **Parathyroid glands** usually lie between posterior border of thyroid gland and its sheath (usually 2 on each side of the thyroid), often just lateral to anastomosis between vessel joining superior and inferior thyroid arteries
- **Internal jugular vein** and **common carotid artery** lie postero-lateral to thyroid
Anatomy

- Each lobe
  - pear-shaped and ~5cm long
  - extends inferiorly on each side of trachea (and oesophagus), often to level of 6th tracheal cartilage

- Attached to arch of cricoid cartilage and to oblique line of thyroid cartilage
  - moves up and down with swallowing and oscillates during speaking
Blood supply

- highly vascular
- main supply from *superior and inferior thyroid arteries*
- usually 3 pairs of veins drain venous plexus on anterior surface of thyroid
Lymphatic drainage

- Lymphatics run in the interlobular connective tissue, often around arteries
- Pass to prelaryngeal LN’s → pretracheal and paratracheal LN’s
Thyroid Gland

HISTOLOGY
Histology

- Functional units are **follicles** – responsible for synthesis and secretion of $T_3$ and $T_4$
- Occasional scattered “clear cells”/parafollicular cells/“C cells” produce and secrete **calcitonin**
- **Colloid** is the secretory product of follicular cells
  - Extra-cellular proteinaceous substance composed of thyroid hormones linked together with protein (“thyroglobulin”)
Histology
Thyroid Gland

PHYSIOLOGY
Thyroid hormones – structure

- 2 principal thyroid hormones
  - thyroxine \( (T_4) \) or tetraiodothyronine
  - triiodothyronine \( (T_3) \)
Physiology

- Produce T4 and T3
- Hypothalamus releases thyroid releasing factor (TRF) to pituitary, which releases thyroid stimulating hormone (TSH) into blood
- Follicular cells normally synthesize thyroglobulin and secrete it into the follicular lumen
Physiology

- Thyroid peroxidase, found in apical membrane of thyroid follicular cells, catalyzes iodination of tyrosine residues on thyroglobulin molecule and coupling of iodotyrosyl residues to form T4 (thyroxine) and T3, which are still bound to thyroglobulin, making them inactive; they are then stored as colloid.
Physiology

- In response to TSH, follicular cells pinocytose colloid, release the thyroglobulin, and secrete now active T4 and T3 into bloodstream.
- Body needs 100 mg of iodide per day from diet to synthesize adequate T4.
- Most T4/T3 is reversibly bound to thyroid binding globulin.
Physiology

- Free T4/T3 enters cells, binds to nuclear receptors, increases basal metabolic rate
- Decreased serum T4/T3 stimulates release of TRF and TSH via negative feedback regulation; elevated levels have opposite effect
Thyroid regulation
Thyroid hormones – structure

- Thyroid hormones stored conjugated to thyroglobulin, but are cleaved by pinocytosis before being released into circulation.
- Majority of the thyroid hormone secreted is T₄ (90%), but T₃ is the considerably more active hormone.
- Although some T₃ is also secreted, most is derived by deiodination of T₄ in peripheral tissues, especially liver and kidney.
- Deiodination of T₄ also yields reverse T₃ (no known metabolic activity).
- Both are poorly water soluble.
- 99% of circulating thyroid hormone is bound to carrier protein (mostly thyroxine-binding globulin, but also transthyrein and albumin).
  - Provides a stable pool from which unbound/free hormone is released for uptake by target organs.
Thyroid hormones – function

- Likely that all cells express thyroid hormone receptors
- Metabolism
  - Increases basal metabolic rate
  - Increases carbohydrate and lipid metabolism
- Normal growth
- Normal development
  - Especially CNS
- Other systems
  - CVS – increases heart rate, cardiac output
  - CNS – mental acuity
  - Reproduction – fertility requires normal thyroid function
Calcitonin – function

- Minor role in regulating (reducing) blood calcium concentration
  - Suppresses osteoclastic bone resorption
  - Inhibits renal tubular reabsorption of calcium and phosphorus
Effects of TSH on thyroid gland

- Increased thyroglobulin proteolysis → increased circulating thyroid hormones
- Increased activity of “iodide pump” - increases cellular iodine uptake
- Increased iodination of tyrosine and coupling
- Increased size and secretory activity of thyroid cells
- Increased number of thyroid cells, plus change from cuboidal to columnar epithelial structure
Thyroid Gland

PATHOLOGY
Hypothyroidism

- Deficiency in thyroid hormone secretion and action
- Common, 2-15%
- Clinical symptoms:
  - Obvious: lethargy, fatigue, cold intolerance
  - Subtle
- Primary: impaired synthesis of T4 & T3
- Secondary: decreased in TRH, TSH
## Hypothyroidism

<table>
<thead>
<tr>
<th>Cause</th>
<th>Hormone concentrations</th>
<th>Goitre</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary failure of thyroid gland</td>
<td>↓$T_3$ and $T_4$, ↑TSH</td>
<td>Yes</td>
</tr>
<tr>
<td>Secondary to hypothalamic or pituitary failure</td>
<td>↓$T_3$ and $T_4$, ↓TSH and/or ↓TRH</td>
<td>No</td>
</tr>
<tr>
<td>Dietary iodine deficiency</td>
<td>↓$T_3$ and $T_4$, ↑TSH</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Hyperthyroidism

- Hypermetabolic condition caused by excessive production of thyroid hormones
- Most common
  - Grave’s Disease
Grave’s disease

- Most important cause of hyperthyroidism
- Autoimmune thyroiditis
- Diffuse thyroid enlargement and exophthalmos
- Follicular cells stimulated by IgG antibody (LATS) that causes constant thyroid hormone production, independent of TSH
- Large, fleshy thyroid gland with large follicles lined by active cells
## Hyperthyroidism

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<td>Abnormal thyroid-stimulating immunoglobulin (eg. Grave’s disease)</td>
<td>↑ T&lt;sub&gt;3&lt;/sub&gt; and T&lt;sub&gt;4&lt;/sub&gt;, ↓ TSH</td>
<td>Yes</td>
</tr>
<tr>
<td>Secondary to excess hypothalamic or pituitary secretion</td>
<td>↑ T&lt;sub&gt;3&lt;/sub&gt; and T&lt;sub&gt;4&lt;/sub&gt;, ↑ TSH and/or ↑ TRH</td>
<td>Yes</td>
</tr>
<tr>
<td>Hypersecreting thyroid tumour</td>
<td>↑ T&lt;sub&gt;3&lt;/sub&gt; and T&lt;sub&gt;4&lt;/sub&gt;, ↓ TSH</td>
<td>No</td>
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THYROID FUNCTION TESTS
TSH, T4 & T3
Thyroid regulation
TSH

- In most reference laboratories, the normal range for TSH is 0.45 to 4.5 mIU/L.
- Very reliable assays with a wide dynamic range.
- An integrated measure of thyroid hormone action.
- The response of TSH to changing thyroid hormone levels is greatly amplified.
- It’s not affected by any binding protein changes.
TSH

- an indirect measure of thyroid function
- there is some delay in responses to acute changes in peripheral thyroid hormone levels
- in a very rare case (pituitary or hypothalamic disease, or thyroid hormone resistance) the TSH measurement alone can be misleading
Total T4

- Normal range for total T4 is 5.5 to 12.5 microgram/dL (206 to 309 nanomol/L)
- Pretty reliable
- Good measure of thyroid gland output
- Changes occur fast when thyroid gland activity changes
Total T4

- Concentration is highly variable, and highly dependent on the variable thyroid hormone-binding globulin concentrations.
- A small fraction is free and that’s actually the biologically active fraction.
- The assays have limitation of being all competitive assays and suffering from a limited dynamic range.
Total T3

- normal range for total T3 is 60 to 180 nanograms/dL (0.92 to 2.76 nanomol/L)
- reliable assays
- represents the active thyroid hormone
- changes occur fast with changes in thyroid gland activity
- selectively overproduced in thyrotoxicosis
Total T3

- Concentration is linked to the highly variable thyroid hormone-binding globulin concentrations.
- Only a small free fraction is biologically active.
- Majority of T3 is manufactured in peripheral tissues on demand.
- Competitive assays with limited dynamic range.
FreeT4

- Typical normal range for FT4 is 0.9 to 2.3 nanograms/dL (12 to 30 picomol/L)
- reasonable reliable
- give a good measure of the thyroid gland hormone output
- change fast with thyroid gland activity
- and, most importantly, are independent of TBG concentrations
FreeT4

- it is a pro-hormone—the active hormone is T3, and levels can occasionally fluctuate with non-thyroidal illness
- standard assays have a very limited dynamic range and at some ranges of binding protein concentrations, they may be unreliable
Free T3

- Normal range for FT3 is 230 to 420 picograms/dL (2 to 7 picomol/L)
- the same advantages, more or less, as free T4 and very similar disadvantages.
- the major disadvantages
  - all current free T3 assays have serious shortcomings and generally are not recommended
Free T3

- Free thyroxine concentrations are already only a few percent of the total thyroxin concentrations.
- Free T3 concentrations are only a few percent of the total T3 concentrations:
  - The total T3 concentrations are never more than 20% of the total thyroxin concentration.
  - Low picomolar concentrations, which causes a lot of analytical problems.
Balancing It All Up

What Test to Use and When
For initial diagnosis

- **TSH**
  - It is equally useful for hypo- and hyperthyroidism
  - has the highest sensitivity and specificity for initial diagnosis
  - and is least likely to be disturbed by non-thyroidal illness or drugs
For initial diagnosis

- TSH

- Free T4:
  - free T4 measurements are often used when either the TSH alone is not clearly diagnostic (i.e., borderline measurements)
  - or when there is some need to gauge the severity of hypo- or hyperthyroidism
For initial diagnosis

- TSH
- Free T4
- Total T3:
  - those cases where both TSH and FT4 measurements are on the fence, or not clearly diagnostic
Follow up patients

- Acute & sub-acute conditions:
  - Graves’ disease or sub-acute thyroiditis
    - measure FT4 because the changes in thyroid hormones can occur very rapidly and the TSH levels may lag a few days or even weeks behind
    - TSH
    - Total T3
Follow up patients

- Chronic or slowly progressive conditions:
  - permanent hyperthyroidism and NG:
    - TSH is the main stay
    - Occasionally supplemented by Free T4
    - Rarely by Total T3
Thyroid Gland

PATHOLOGY
Thyroid regulation

Diagram illustrating the thyroid regulation pathway:

1. Hypothalamus secretes TRH (Thyrotropin-Releasing Hormone)
2. TRH stimulates the pituitary gland to release TSH (Thyroid-Stimulating Hormone)
3. TSH stimulates the thyroid gland to produce T4 (Thyroxine) and T3 (Triiodothyronine)
4. T4 and T3 are released into the bloodstream
5. T4 and T3 exert stimulatory effects on peripheral tissues
6. T4 and T3 also inhibit the production of TRH and TSH, creating a feedback loop

Key terms:
- TRH
- TSH
- Thyroid hormone
- Peripheral tissues
- T4 & T3

Feedback mechanisms include:
- Negative feedback inhibition
- Stimulatory effect
- Inhibitory effect
Low TSH – with a high FT4 and/or FT3

- Suggestive of hyperthyroidism
- Subacute or granulomatous thyroiditis
- Other causes include factitious thyrotoxicosis (caused by excessive use of thyroid hormone medication)
Low TSH – with a low FT4 and/or FT3

- secondary (central) hypothyroidism
- nonthyroid illness (sick euthyroid syndrome)
- in the second and third trimesters of pregnancy
Low TSH –
with a normal FT4 and/or FT3

- suggest subclinical (mild) hyperthyroidism
- nonthyroid illness
- the following drugs:
  - dopamine, dopaminergic agonists, glucocorticoids, cytokines, or octreotide
- recent treatment of hyperthyroidism with antithyroid medication
- in the first trimester of pregnancy
High TSH – with a high FT4 and/or FT3

- assay artifact/laboratory error
- TSH-secreting pituitary tumor
- resistance to thyroid hormonehyper- or hyposecretion of other pituitary hormones
- thyroid hormone resistance syndrome
- Thyroxine replacement therapy
- acute psychiatric disorders
High TSH – with a low FT4 and/or FT3

- suggests primary hypothyroidism.
  - autoimmune thyroiditis (Hashimoto disease),
    - the most common cause of primary hypothyroidism.
    - More than 90% have positive TPOAb
- thyroidectomy or radioactive iodine treatment of the thyroid without adequate thyroid hormone replacement
High TSH – with a normal FT4 and/or FT3

- subclinical (mild) hypothyroidism
- recovery from nonthyroid illness
- poor adherence to thyroxine replacement therapy or its malabsorption
- medication that promotes increased metabolism of thyroid hormone
- problems with assay procedures
  - (e.g., interference of abnormal antibodies in serum) can cause false elevation in TSH
Normal TSH – with a low FT4 and/or FT3

- secondary (central) hypothyroidism
- drug use (e.g., phenytoin, rifampin, carbamazepine, barbiturates)
- and assay error when interfering substances are present.
Sensitive serum TSH

- **TSH**
  - **Undetectable**
  - **Subnormal**
  - **Normal**
  - **Elevated**
    - **Hyperthyroid**
      - Free T4, T3 if FT4 is NL
    - **Borderline status**
      - Free T4 & free T3
    - **No further tests**
    - **Hypothyroid**
      - Free T4
  - **TRH test**
Auxiliary Testing

- Antithyroperoxidase autoantibodies
- Antithyroglobulin autoantibodies
- Anti-TSH-receptor autoantibodies
- Thyroid hormone-binding protein
- Molecular analysis of thyroid hormone receptors
Summary - thyroid

- Major endocrine gland
- Located in the neck
- Closely related to parathyroid glands, thyroid cartilage, trachea, important nerves (recurrent laryngeal) and vessels
- Important role in metabolic regulation via thyroid hormones
  - $T_3$ and $T_4$
  -Stored extracellularly in inactive form
Summary

- Regulated by feedback loop involving hypothalamus (TRH), pituitary (TSH) and thyroid hormones themselves.
- Hypo- and hyperthyroidism are common conditions.
- Benign and malignant pathological conditions:
  - Grave’s disease
  - Hashimoto’s disease
  - Papillary/follicular/anaplastic carcinoma
  - Medullary carcinoma
Thyroid Gland

PATHOLOGY
Thyroid pathology

- Thyroid enlargement may be diffuse or nodular
  - Irregular multinodular enlargement (goitre) of the entire gland is common, especially in the elderly
  - Focal nodular enlargement may be due to a tumour
  - Symmetrical slightly nodular (‘bosselated’) firm enlargement of the whole gland is characteristic of Hashimoto’s disease
  - Symmetrical diffuse enlargement is usually associated with hyperthyroidism (e.g. Grave’s disease)

- Most thyroid enlargement (except Hashimoto’s) results from hyperplasia of thyroid follicles and their cells
Multinodular goitre

- Common in the elderly
- Often undetected
- May present for cosmetic reasons (neck swelling) or compression symptoms (eg. trachea)
- Usually have normal thyroid function
- Cause uncertain
  - Uneven response of thyroid tissue to fluctuating TSH levels over many years
Thyroiditis

- **Viral**
  - De Quervain’s thyroiditis
    - Affects younger/middle-aged women
    - Slight diffuse, tender swollen gland
    - Transient febrile illness, often viral origin (e.g. mums with kids who have mumps/measles etc)
    - Inflammatory destruction of follicular cells

- **Autoimmune**
  - Grave’s disease
  - Hashimoto’s disease
Thyroiditis

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Grave’s disease

- Most important cause of hyperthyroidism
- Autoimmune thyroiditis
- Diffuse thyroid enlargement and exophthalmos
- Follicular cells stimulated by IgG antibody (LATS) that causes constant thyroid hormone production, independent of TSH
- Large, fleshy thyroid gland with large follicles lined by active cells
Hashimoto’s disease

- Destructive autoimmune thyroiditis
- Common in middle age, women > men
- Most common auto-antibodies are anti-microsomal Ab and anti-thyroglobulin Ab
- Diffusely enlarged thyroid, symmetrical and firm
Thyroid malignancies

- Follicular cell origin
  - Papillary carcinoma - 70%
  - Follicular carcinoma - 25%
  - Anaplastic carcinoma - rare

- Parafollicular ‘C’ cell origin
  - Medullary carcinoma - 5%
Papillary carcinoma

- Follicular cell origin
- Well-differentiated
- Arises mostly in young adults
- Often multifocal
- Metastasises via lymphatics to neck nodes
- Slow-growing
- Excellent prognosis

Treatment
- Surgery - lobectomy/thyroidectomy
- Iodine-131
- ± EBRT
Follicular carcinoma

- Follicular cell origin
- Most common in middle age
- Metastasises via blood stream
  - Characteristically spreads to bone, lung
- Good prognosis

Treatment
- Surgery
- Iodine-131
- ± EBRT
Anaplastic carcinoma

- Follicular cell origin
- Occurs exclusively in the elderly
- Poorly differentiated
- Rapidly progressive with direct invasion of adjacent structures
- Very poor prognosis
- Treatment - poor response
  - Surgery?
  - EBRT?
  - (Iodine-131?)
Medullary carcinoma

- Arises in parafollicular ‘C’ cells
- Sporadic or part of MEN syndrome
- Small cells containing neuro-endocrine granules
- Occurs in middle-aged and elderly
- Slow-growing
- Metastasises to lymph nodes
- Secretes calcitonin (blood test)

Treatment
- Surgery
- EBRT (but relatively radio-resistant)
- Low uptake of iodine-131 - limited role