Hyperthyroidism
Hypothyroidism

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History

• 2700 BC in China – seaweed for goiter
• 300 BC Hindu holy texts discuss goiter
• 40 BC in Ancient Rome – epidemics of goiter in Alps, burnt seaweed for treatment
• 150 AD Galenos – burnt sponge for goiter
• 650 AD in China – Sun Ssu-Mo used powdered mollusc shells and chopped up thyroid glands for goiter
• 990 AD – Ali-Ibn-Abbas discussed surgery as a treatment for goiter
• 1100 AD – **Exophtalmus** associated with goiter
History

- 1475 – Wang Hei, *dried thyroid* for treatment of goiter
- 1543 – Vesalius describes anatomy of thyroid
- 1602 – first description of *cretins*
- 1656 – Thomas Wharton named it *thyroid gland*
- 1789 – Association between goiter and cretenism
- 1811 – Iodine in seaweed as active ingredient
- 1820 – treatment of goiter with iodine
- 1880s – Kocher describes that *total thyroidectomy* causes hypothyroidism, treatment is sheep thyroid
- 1914 – Kendall isolated *thyroxine*
- 1952 – *tri-iodothyronine* synthesized
• Thureos (Greek) – oblong shield, door
• Thyroid gland – shield-shaped gland
Aberrant and normal locations of thyroid tissue

- Lingual
- Intralingual
- Thyroglossal tract
- Sublingual
- Thyroglossal cyst
- Prelaryngeal
- Normal
- Intratracheal
- Substernal

Linguval thyroid

Scintigram; lingual thyroid
Iodine

- Iodide uptake is a critical first step in thyroid hormone synthesis
- 150 ug – daily intake of iodine
- 125 ug – taken up by the thyroid gland
- Ingested iodide is bound to serum proteins, particularly albumin
- Unbound iodide is excreted in the urine
Thyroid hormones

• Triiodothyronine (T3) and thyroxine (T4)
• Produced by follicular cells from the precursor thyroglobulin
• **Thyroid peroxidase** bounds iodine to tyrosine residues in thyroglobulin forming:
  • Monoiodotyrosine (MIT)
  • Diiodotyrosine (DIT)
• DIT + DIT = T4
• MIT + DIT = T3
• Proteases digest iodinated thyroglobulin, releasing T3, T4
• T4 is converted to T3 by **iodothyronine deiodinase** in the periphery
Circulation and transport

• 99% bound to transport proteins (inactive), <1% free
• Transport proteins increase the pool of circulating hormones, delay hormone clearance and modulate hormone delivery to selected tissues
• Thyroxin-binding globulin TBG (70%)
• Transthyretin TTR / thyroxin-binding prealbumin TBPA (15%)
• Albumin (15%)
• Unbound fT4 (0,03%)
• Unbound fT3 (0,3%)
Receptors

- Membrane bound receptors
Circulation and transport

- Membrane transport by active iodothyronine transporters (10 different transporters identified to date)
- Intracellular transport
- Thyroid hormone receptors bind to thyroid hormone response elements (TREs) as heterodimers with retinoic acid
Calcitonin

- Produced by parafollicular C-cells
- Secretion is stimulated by increase in serum Ca$^{2+}$
- Reduces blood Ca$^{2+}$ (counteracts PTH)
  - Inhibition of absorption in intestines
  - Inhibits osteoclast activity in bones
  - Stimulates osteoblast activity in bones
  - Inhibits renal tubular reabsorption of Ca$^{2+}$
- Inhibits phosphate reabsorption by kidney tubules (mirrors PTH)
- Treatment of hypercalcemia and osteoporosis
Parathyroid glands
Parathyroid glands

- Parathyroid hormone
  - An antagonist of calcitonin
  - Increase in plasma Ca$^{2+}$
Parathyroid hormone

[Diagram showing the effects of parathyroid hormone on calcium homeostasis, including changes in calcium and phosphate levels in bone, kidney, and gut.]
Hyperparathyroidism

• Primary (4/100000; women; age>45)
  • Parathyroid glands

• Secondary
  • Kidneys

• Tertiary
  • From secondary – autonomy of the parathyroid glands

• Bone resorption
Hypercalcemia

- Symptoms
  - Renal (stones, polydipsia, polyuria)
  - Bones (pain)
  - Gut (constipation)
  - Brain (depression, fatigue, anorexia)

- Signs
  - Hypertension, cognitive impairment, joint swelling, bone deformities
Hypercalcemia

• Causes
  • Primary (tertiary) hyperparathyroidism
  • Malignancies (parathyroid hormone-related protein)
  • Hypervitaminosis D
  • Renal failure

• Therapy
  • Diuretics
  • Bisphosphonates
  • Calcitonin
<table>
<thead>
<tr>
<th>Condition</th>
<th>Serum Ca²⁺</th>
<th>Serum Pi</th>
<th>Serum PTH</th>
<th>Serum 25(OH)D</th>
<th>Serum 1,25(OH)₂D</th>
<th>Associated findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary hyperparathyroidism</td>
<td>↑</td>
<td>N or ↓</td>
<td>High N or ↑</td>
<td>N</td>
<td>N or ↑</td>
<td>80% Asymptomatic Nephrolithiasis, Osteoporosis, Hypercalcemic sx</td>
</tr>
<tr>
<td>Cancer with extensive bone metastases</td>
<td>↑</td>
<td>N or ↑</td>
<td>↓</td>
<td>N</td>
<td>↓ or N</td>
<td>History of primary tumor, destructive lesions on radiograph, bone scan</td>
</tr>
<tr>
<td>Multiple myeloma and lymphoma</td>
<td>↑</td>
<td>N or ↑</td>
<td>↓</td>
<td>N</td>
<td>↓ or N</td>
<td>Abnormal serum or urine protein electrophoresis, abnormal bone radiographs</td>
</tr>
<tr>
<td>Humoral hypercalcemia of malignancy</td>
<td>↑</td>
<td>N or ↓</td>
<td>↓</td>
<td>N</td>
<td>↓ or N</td>
<td>↑PTHrP, Solid malignancy usually evident</td>
</tr>
<tr>
<td>Sarcoidosis and other granulomatous diseases</td>
<td>↑</td>
<td>N or ↑</td>
<td>↓</td>
<td>N</td>
<td>↑</td>
<td>Hilar adenopathy, interstitial lung disease, elevated angiotensin-converting enzyme</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>↑</td>
<td>N</td>
<td>↓</td>
<td>N</td>
<td>N</td>
<td>Symptoms of hyperthyroidism, elevated serum thyroxine</td>
</tr>
<tr>
<td>Vitamin D intoxication</td>
<td>↑</td>
<td>N or ↑</td>
<td>↓</td>
<td>Very ↑</td>
<td>N or ↑</td>
<td>History of excessive vitamin D intake</td>
</tr>
<tr>
<td>Milk—alkali syndrome</td>
<td>↑</td>
<td>N or ↑</td>
<td>↓</td>
<td>N</td>
<td>N or ↓</td>
<td>History of excessive calcium and alkali ingestion, heavy use of over-the-counter calcium-containing antacids</td>
</tr>
<tr>
<td>Total body immobilization</td>
<td>↑</td>
<td>N or ↑</td>
<td>↓</td>
<td>N</td>
<td>↓ or N</td>
<td>Multiple fractures, paralysis (children, adolescents, patients with Paget disease of bone)</td>
</tr>
</tbody>
</table>
Hypocalcemia

• Symptoms & Signs
  • Tetany, paresthesia, ECG changes

• Causes
  • Hypoparathyroidism (inborn, post surgery), low calcium intake, hypovitaminosis D, renal failure

• Therapy
  • Calcium, vitamin D
Hypocalcemia
Hyperthyroidism

- Excess production and release of thyroid hormone by the thyroid gland resulting in high serum levels
Thyrotoxicosis

- Clinical state that results from *inappropriately high thyroid hormone levels in tissues*
- Hypothyroidism is a form of thyrotoxicosis
- **Extrathyroidal sources**
  - exogenous intake
  - release of preformed stored hormone

- Clinical presentation variable:
  - Subclinical (suppressed TSH levels, normal T3 and T4)
  - Life-threatening – thyroid storm
- Prevalence 1.2% (0.7% subclinical)
## Table 1

### Symptoms and signs of thyrotoxicosis

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
<th>Differential Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight loss despite eating</td>
<td>Thin, cachectic</td>
<td>DM, malabsorption, CHF</td>
</tr>
<tr>
<td>Heat intolerance, sweating</td>
<td>Diaphoresis, hyperthermia</td>
<td>Hypermetabolic state (pheo, carcinoid), malignancy, infection</td>
</tr>
<tr>
<td>Nervousness, restlessness</td>
<td>Anxious appearing</td>
<td>Anxiety, pheo, islet cell tumor</td>
</tr>
</tbody>
</table>

### Head, Eyes, Ears, Nose, and Throat

| Neck swelling | Goiter | Thyromegaly, infection |
| Eyelid swelling, redness, double vision | Proptosis, chemosis, conjunctival injection, lid lag | Ophthalmopathy, conjunctivitis, cellulitis |
| Palpitations | Tachycardia, atrial fibrillation | Arrhythmia, pheo, anxiety, drug induced |

### Respiratory

| Dyspnea | Tachypnea | CHF, angina, deconditioning |

### Gastrointestinal

| Diarrhea, nausea, vomiting | Abdominal tenderness | Gastroenteritis, malabsorption, IBS |

### Neuromuscular

| Difficulty rising from chair, difficulty combing hair | Proximal muscle weakness | Myopathy |
| Extremity shaking | Tremor | Medication side effect, idiopathic |

### Skin

| Discoloration | Thickening | Pretibial myxedema, Addison disease |

### Genitourinary/Endocrine

| Amenorrhea, oligomenorrhea | Gynecomastia | Gynecologic disorder |
| Breast enlargement | | Idiopathic, estrogen excess |

### Table 2

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Prevalence, % ^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>70</td>
</tr>
<tr>
<td>Weight loss (poor appetite)</td>
<td>60</td>
</tr>
<tr>
<td>Heat Intolerance</td>
<td>55</td>
</tr>
<tr>
<td>Tremulousness</td>
<td>55</td>
</tr>
<tr>
<td>Palpitations</td>
<td>50</td>
</tr>
<tr>
<td>Diaphoresis (heat Intolerance)</td>
<td>45</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>40</td>
</tr>
<tr>
<td>Nervousness (anxiety)</td>
<td>40</td>
</tr>
<tr>
<td>Hyperdefecation</td>
<td>20</td>
</tr>
<tr>
<td>Neck fullness</td>
<td>20</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>10</td>
</tr>
<tr>
<td>Eye symptoms (pain, redness, swelling, diplopia)</td>
<td>10</td>
</tr>
<tr>
<td>Weight gain</td>
<td>10</td>
</tr>
</tbody>
</table>

### Physical findings

| Tachycardia | 80 |
| Diffuse palpable goiter with an audible bruit | 70 |
| Increased pulse pressure | 50 |
| Tremor | 40 |
| Warm moist palms | 35 |
| Periorbital edema and proptosis | 25 |
Causes

- Diffuse toxic goiter – Graves disease 75%
- Toxic multinodular goiter – Plummer disease
- Toxic adenoma
- Thyroiditis
- Gestational – due to HCG
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Clinical Findings</th>
<th>Laboratory Results</th>
<th>Imaging Findings</th>
<th>Other Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graves disease</td>
<td>Diffuse goiter, orbitopathy</td>
<td>Increased FT$_4$ and T$_3$, low TSH, positive TSH-receptor antibody</td>
<td>Elevated 24-h RAI uptake (often &gt;30%-50%), diffuse uptake on scan, increased vascularity on Doppler-flow ultrasound</td>
<td>Typically seen in younger age groups and women</td>
</tr>
<tr>
<td>Toxic multinodular goiter</td>
<td>Multinodular goiter</td>
<td>Increased FT$_4$, T$_3$, or both</td>
<td>Multiple hyperfunctioning nodules on imaging</td>
<td>More common in older persons, women, and in areas of relative iodine deficiency</td>
</tr>
<tr>
<td>Solitary toxic nodule</td>
<td>Large (&gt;3 cm) solitary thyroid nodule</td>
<td>Increased FT$_4$, T$_3$, or both</td>
<td>Solitary hyperfunctioning nodule with suppression of the parafollicular tissue and contralateral lobe</td>
<td>More common in older persons, women, and in areas of relative iodine deficiency</td>
</tr>
<tr>
<td>Painless thyroiditis</td>
<td>Mild hyperthyroidism and small nonpainful goiter; self-limited condition (usually &lt;2-3 mo)</td>
<td>Variable elevation of FT$_4$ (often 1.6-2.0 × ULN), increased T$_3$ (often 1.0-1.5 × ULN), very high ESR (typically &gt;50 mm/h)</td>
<td>Absent to very low (0%-5%) 24-h RAI uptake</td>
<td>Has a predilection for the postpartum period and is also associated with lithium use; may recur over years</td>
</tr>
<tr>
<td>Subacute de Quervain thyroiditis</td>
<td>Painful enlarged thyroid that often occurs after an upper respiratory tract infection</td>
<td>Variable elevation of FT$_4$ (often 1.6-2.0 × ULN), increased T$_3$ (often 1.0-1.5 × ULN), very high ESR (typically &gt;50 mm/h)</td>
<td>Absent to very low (0%-5%) 24-h RAI uptake</td>
<td>Usually not associated with permanent sequelae</td>
</tr>
<tr>
<td>Drug-Induced thyroiditis</td>
<td>Mildly enlarged thyroid</td>
<td>Variable elevation of FT$_4$ (often 1.6-2.0 × ULN), increased T$_3$ (often 1.0-1.5 × ULN)</td>
<td>Absent to very low (0%-5%) 24-h RAI uptake</td>
<td>Associated with use of amiodarone, lithium, Interferon-α, sorafenib, and other multikine inhibitors</td>
</tr>
<tr>
<td>Iodine-Induced hyperthyroidism</td>
<td>Hyperthyroidism in days to months after iodine exposure in patients with preexisting thyroid disease, typically a multinodular goiter</td>
<td>Variable elevation of FT$_4$ (often 1.6-2.0 × ULN), increased T$_3$ (often 1.0-1.5 × ULN)</td>
<td>Absent to very low (0%-5%) 24-h RAI uptake</td>
<td>Associated with iodine exposure usually in the form of amiodarone or iodinated contrast agents</td>
</tr>
<tr>
<td>Ingestion of thyroid hormone</td>
<td>Thyrotoxic symptoms and signs without an enlarged thyroid</td>
<td>Elevated T$_4$ and T$_3$ in patients ingesting T$_4$; elevated T$_3$ in patients ingesting T$_3$</td>
<td>Absent to very low (0%-5%) 24-h RAI uptake</td>
<td>May be intentional or inadvertent</td>
</tr>
<tr>
<td>Struma ovarii</td>
<td>Thyrotoxic symptoms and signs without an enlarged thyroid</td>
<td>Elevated FT$_4$ and T$_3$</td>
<td>Increased RAI uptake over the pelvis</td>
<td>May rarely be malignant</td>
</tr>
<tr>
<td>Molar pregnancy and chorocarcinoma</td>
<td>Thyrotoxic signs and symptoms with an enlarged thyroid</td>
<td>Elevated FT$_4$ (often 1.6-2.0 × ULN) and T$_3$ (often 1.6-2.0 × ULN)</td>
<td>Elevated 24-h RAI uptake (&gt;30%-50%)</td>
<td>Caused by high levels of hCG, which has thyroid-stimulating action when present in high serum concentrations</td>
</tr>
</tbody>
</table>

Abbreviations: ESR, erythrocyte sedimentation rate; FT$_4$, free thyroxine; hCG, human chorionic gonadotropin; RAI, radioactive iodine; T$_3$, triiodothyronine; T$_4$, thyroxine; TPO, thyroid peroxidase; TSH, thyrotropin (thyroid-stimulating hormone); ULN, upper limit of normal.
Thyroid storm

- Life-threatening form of thyrotoxicosis that is usually triggered by medical crisis, surgery, infection, sepsis, pregnancy, heart attack
- **Exaggerated** signs and symptoms of thyrotoxicosis
- **Altered mental state** – agitation, emotional lability, delirium, convulsions, chorea-like movements
- **Hyperthermia**, hypertension, dysrhythmia
- Cardiovascular collapse
Goiter

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No palpable or visible goiter</td>
</tr>
<tr>
<td>1</td>
<td>Palpable goiter</td>
</tr>
<tr>
<td></td>
<td>A. Only palpable</td>
</tr>
<tr>
<td></td>
<td>B. Palpable and visible with the neck extended</td>
</tr>
<tr>
<td>2</td>
<td>Goiter visible with neck in normal position</td>
</tr>
<tr>
<td>3</td>
<td>Very large goiter visible from distance</td>
</tr>
</tbody>
</table>
1. Grave’s disease

- Autoimmune disorder
- **Anti-TSH receptor antibodies** that stimulate TSH receptor on follicular cells to produce thyroid hormones
- Prevalence 0.5%, incidence 20 per 100 000 per year
- Women aged 40-60 at highest risk
- Genetic factors account for 80% of the risk of GD
- Other factors - smoking, stress, postpartum state
- Signs and symptoms of hyperthyroidism
- Unique extrathyroidal manifestations
- **Diffuse goiter**
Diffuse goiter of moderate size

Diffuse enlargement and engorgement of thyroid gland (broken line indicates normal size of gland)

Diffuse hyperplasia

Hyperplasia with lymphocytic infiltration
Perspiration
Facial flushing
Loss of weight
Palpable lymph nodes
Shortness of breath
Breast enlargement (Gynecomastia in male)
Warm, velvety skin
Muscle wasting
Rapid pulse
Warm and moist palms
Oligomenorrhea or amenorrhea
Localized myxedema
Nervousness
Excitability
Restlessness
Emotional instability
Insomnia
Exophthalmos
Goiter (may have thrill and bruit)
Increased appetite
Diarrhea (occasional)
Tremor
Clubbing of fingers (in some patients with severe exophthalmos)
Palpitation, tachycardia
Muscular weakness, fatigability
Grave’s ophthalmopathy

- Upper eyelid retraction
- Lid lag
- Edema
- Lagophthalmos
- Erythema
- Conjunctivitis
- Bulging eyes
Moderately severe ophthalmopathy

Testing for resiliency

Severe progressive ophthalmopathy
Diagnosis

- TSH ↓
- Free T4 and T3 ↑
- Total T3 ↑

- **TSH receptor antibodies**
- Thyroglobulin and thyroid peroxidase antibodies
- Radioiodine uptake (I 131), Scintigraphy (Tc 99m)
- Ultrasonography
Treatment

• Goals:
  • To restore normal thyroid function
  • To avoid recurrence of hyperthyroidism
  • To prevent development of hypothyroidism
  • To prevent *de novo* occurrence or progression of Grave’s ophthalmopathy

• 3 standard approaches:
  • Antithyroid drugs
  • 131I-radiotherapy
  • Surgery - thyroidectomy
Antithyroid drugs

• Direct or indirect immunosuppressive effects
• Main mode of action – decrease of excess thyroid hormone by inhibition of thyroid peroxidase

• Methimazole
• Carbimazole
• Propylthiouracil (also in pregnant women)

• Beta-blockers to reduce hyperthyroid symptoms
131I-radiotherapy

• Gradual necrosis of thyroid cells
• Eventually results in hypothyroidism in 80% of patients in 2-3 months after single administration
• Low doses associated with high rate of recurrence
Thyroidectomy

- Definitive treatment
- Complications:
  - Hypoparathyroidism
  - Palsy of the recurrent laryngeal nerve
  - Wound infections
Primary treatments for Graves Disease

Antithyroid drugs (methimazole)

Radioactive iodine (RAI)

Total thyroidectomy

**Iodide uptake**

**TPO**

**ATD**

**TPO-I^+**

**Decreased T3 and T4 release**

**β particle emission**

**Cell necrosis**

**TRAb**

**Free T4**

**Free T3**

**Months**

0  6  12

**Level**

**Normal range**

**Methimazole** (12-18 mo)

**RAI**

**Levothyroxine replacement**

**Methimazole** (1-3 mo)

**Levothyroxine replacement**

**Surgery**
2. Toxic multinodular goiter

- Excess production of thyroid hormones from functionally autonomous thyroid nodules that do not require stimulation from TSH
- Thyrotoxicosis + nodules
Toxic multinodular goiter

- Hyperplastic response of the entire thyroid gland to a stimulus (iodine deficiency)
- Nodules arise from pre-existing goiter
- Autonomous thyroid nodules become hyper-functional from mutations in the follicular cell – increased cell function and growth
- Different from Grave’s disease
- Antithyroid medication, radioactive iodine, surgery
- Incidence increases with age and iodine deficiency
3. Toxic adenoma

- Neoplasm resulting from a genetic mutation in a single precursor cell
- Single nodule
- If producing excessive hormones - referred to as hot (toxic) adenoma
- If clinically silent – cold or warm adenoma
Hyperthyroidism and Other Causes of Thyrotoxicosis:
Management Guidelines of the American Thyroid Association
and American Association of Clinical Endocrinologists

The American Thyroid Association and American Association of Clinical Endocrinologists
Taskforce on Hyperthyroidism and Other Causes of Thyrotoxicosis

Rebecca S. Bahn (Chair),1,* Henry B. Burch,2 David S. Cooper,3 Jeffrey R. Garber,4 M. Carol Greenlee,5
Irwin Klein,6 Peter Laurberg,7 I. Ross McDougall,8 Victor M. Montori,7 Scott A. Rivkees,9
Douglas S. Ross,10 Julie Ann Sosa,11 and Marius N. Stan1

Guidelines

The 2015 European Thyroid Association
Guidelines on Diagnosis and Treatment of
Endogenous Subclinical Hyperthyroidism

Bernadette Biondia Luigi Bartalena b David S. Cooper c Laszlo Hegedüs d
Peter Laurberg9 George J. Kahaly9
### Benign Nodules (95%)

<table>
<thead>
<tr>
<th>Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperplastic nodules</td>
<td>(85%)</td>
</tr>
<tr>
<td>Adenomas</td>
<td>(15%)</td>
</tr>
<tr>
<td>Cysts</td>
<td>(&lt;1%)</td>
</tr>
</tbody>
</table>

### Carcinomas (5%)

<table>
<thead>
<tr>
<th>Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary</td>
<td>(81%)</td>
</tr>
<tr>
<td>Follicular and Hürthle-cell</td>
<td>(14%)</td>
</tr>
<tr>
<td>Medullary</td>
<td>(3%)</td>
</tr>
<tr>
<td>Anaplastic</td>
<td>(2%)</td>
</tr>
</tbody>
</table>

**Common Varieties of Thyroid Nodules.**
Papillary TC

May have multiple foci

Usually presents as a solitary nonfunctioning nodule

Metastasizes: chiefly to regional lymph nodes (cervical and mediastinal)

Secondary to lungs (miliary spread)

Two different parts of tumor with prominent papillary projections

Rarely to skeleton

Very rarely to brain
Follicular TC

Usually presents as a solitary nonfunctioning nodule

Hematogenous spread to lung and bone

Rare neck lymph node involvement
Medullary TC
Anaplastic TC

- Giant cells
- Spindle cells
- Rapidly growing tender tumor of neck
- Compression and invasion of trachea
MTS to the thyroid

1. Kidney
2. Lung
3. Breast
4. Head and neck malignancy
5. Gastrointestinal tract (colon, esophagus, stomach)
6. Melanoma
Thyroiditis

• Attack on the thyroid resulting in inflammation and damage
• A group of inflammatory disorders with different causes, clinical features, diagnosis, duration, therapy and risks
• Hashimoto’s thyroiditis
• Infection-induced thyroiditis
• Drug-induced thyroiditis
• Radiation-induced thyroiditis
• ...
A short break
Hypothyroidism
Definition

• Lower production and release of thyroid hormones by the thyroid gland resulting in low serum levels
Signs and symptoms of Hypothyroidism

**Psychological**
- Poor memory and concentration
- Poor hearing

**Pharynx**
- Hoarseness

**Heart**
- Slow pulse rate
- Pericardial effusion

**Muscular**
- Delayed reflex relaxation

**Extremities**
- Coldness
- Carpal tunnel syndrome

**General**
- Fatigue
- Feeling cold
- Weight gain with poor appetite
- Hair loss

**Lungs**
- Shortness of breath
- Pleural effusion

**Skin**
- Paresthesia
- Myxedema

**Intestines**
- Constipation
- Ascites

**Reproductive system**
- Menorrhagia
# TABLE 1  Signs and symptoms of hypothyroidism

<table>
<thead>
<tr>
<th>Signs</th>
<th>Symptoms*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothermia</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>Weakness</td>
</tr>
<tr>
<td>Delayed relaxation of deep tendon reflexes</td>
<td>Weight gain</td>
</tr>
<tr>
<td>Periorbital edema</td>
<td>Constipation</td>
</tr>
<tr>
<td>Enlargement of tongue</td>
<td>Cold intolerance</td>
</tr>
<tr>
<td>Diastolic hypertension</td>
<td>Dry skin</td>
</tr>
<tr>
<td>Hair loss</td>
<td>Hoarse voice</td>
</tr>
<tr>
<td>Pleural and pericardial effusions</td>
<td>Edema</td>
</tr>
<tr>
<td></td>
<td>Cognitive dysfunction</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
</tr>
<tr>
<td></td>
<td>Muscle cramps</td>
</tr>
<tr>
<td></td>
<td>Paresthesias</td>
</tr>
<tr>
<td></td>
<td>Menorrhagia</td>
</tr>
<tr>
<td></td>
<td>Dry, gritty-feeling eyes</td>
</tr>
</tbody>
</table>

| Common                                          |                      |
| Fatigue (~ 90%)                                 | Dry, scaly skin (~ 90%)|
| Cold intolerance (~ 80%)                         | Coarse, brittle thinning hair (~ 60%)|
| Depression (~ 70%)                              | Bradycardia (~ 40%) |
| Poor concentration (~ 65%)                       | Hair loss or dryness (~ 70%)|
| Musculoskeletal aches and pains (~ 25%)          | Anemia               |
| Carpal tunnel syndrome (~ 15%)                   | Puffy eyes (~ 90%)   |

| Less common                                      |                      |
| Constipation (~ 50%)                             | Edema (~ 30%)        |
| Hoarse voice (~ 40%)                             | Cerebellar signs*    |
| Menorrhagia (~ 30%)                              | Deafness*            |
|                                                | Psychiatric*         |

* Patients rarely report these symptoms spontaneously. It is therefore important for the clinician to complete a thorough review of systems.
Box 1
Common patient presentations associated with hypothyroidism

Elderly patients
- With new psychiatric complaints
- With cramping, constipation

Patient with combination of weakness, weight gain, and/or hyponatremia

History of depression, weight gain, hoarseness

Young “anemic” woman with frequent episodes of heavy vaginal bleeding

Patient with history of hypertension who develop sudden hypotensive episodes, even after reduction of medication

Refractory hypotension not responsive to routine treatments

Causes

• Central (secondary) – insufficient stimulation by TSH
• Primary – inadequate function of the gland itself (1000x more common than central)
• Congenital
Types of hypothyroidism

<table>
<thead>
<tr>
<th>Type</th>
<th>TSH level</th>
<th>Free T₄ level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary hypothyroidism</td>
<td>Elevated</td>
<td>Low</td>
</tr>
<tr>
<td>Subclinical hypothyroidism</td>
<td>Elevated</td>
<td>Normal</td>
</tr>
<tr>
<td>Secondary hypothyroidism</td>
<td>Normal or low</td>
<td>Low</td>
</tr>
</tbody>
</table>

TSH, thyroid-stimulating hormone; T₄, thyroxine.
Primary hypothyroidism

- After thyroidectomy
- After radioactive iodine to treat Graves disease
- After acute thyroiditis
- After Hashimoto thyroiditis

Central hypothyroidism (hypothalamic or pituitary origin)

- Deficient TSH leads to:
  - Postpartum pituitary infarction
  - Destructive pituitary tumor
  - Isolated deficiency of TSH (e.g., lymphocytic hypophysitis)

Panhypopituitarism

Characteristic facies in hypothyroidism:
- coarse features; thick lips; dry skin;
- puffy eyelids; dull, lethargic expression;
- coarse hair

Macroglossia, showing dental impressions

Pudgy hands; chipped nails; dry, wrinkled skin; hyperkeratosis of elbow
Primary hypothyroidism

- Iodine deficiency – most common cause
- Hashimoto’s thyroiditis – where iodine is sufficient

- Diagnosis based on measurement of TSH and fT4
Hashimoto’s thyroiditis

Thyroid epithelium

T-cell sensitization to thyroid antigens

Helper T-cell

CD8+ cytotoxic T-cell

CD4+ Th1 cell

γ-IFN

Activated macrophages

Thyrocyte injury

T-cell-mediated cytotoxicity

Plasma cell

Anti-thyroid antibodies

Fc receptor

NK cell

Antibody-dependent cell-mediated cytotoxicity

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Pathogenesis

- An autoimmune phenomenon – presentation determined by ratio of antibodies

Thyroid

- Thyroid Stimulating Ab (TSAb)
- Thyroid Stimulation Blocking Ab (TSBAb)

Thyroglobulin Ab

Thyroid peroxidase Ab (anti TPO)

Graves’ Disease

Autoimmune Hypothyroidism (Hashimoto’s)
**Hashimoto thyroiditis**

- **Thyroid peroxidase and thyroglobulin**
- **Antigens**
- **Antibodies**

- B cells in thyroid tissue and extrathyroidal lymphoid tissues

**Microscopy of Hashimoto Thyroiditis**
Mixture of hyperplastic and atrophic follicles with diffuse lymphocytic infiltration

**Riedel thyroiditis**

- **Displacement and/or compression of trachea and esophagus**
- **Enlarged thyroid gland**

**Microscopy of Riedel Thyroiditis**
Macrophage and eosinophilic infiltration with atrophy of follicles (arrows) and marked diffuse fibrosis
Congenital hypothyroidism - cretinism

• 1 in 4000 newborns has severe thyroid deficiency
• If untreated, leads to growth failure and permanent intellectual disability – screening for TSH/T4
• Excessive sleeping
• Poor muscle tone
• Low or hoarse cry
• Infrequent bowel movements
• Jaundice
• Low body temperature
<table>
<thead>
<tr>
<th>Defective Gene Protein</th>
<th>Inheritance</th>
<th>Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROP-1</td>
<td>Autosomal recessive</td>
<td>Combined pituitary hormone deficiencies with preservation of adrenocorticotropic hormone</td>
</tr>
<tr>
<td>PIT-1</td>
<td>Autosomal recessive</td>
<td>Combined deficiencies of growth hormone, prolactin, thyroid-stimulating hormone (TSH)</td>
</tr>
<tr>
<td></td>
<td>Autosomal dominant</td>
<td></td>
</tr>
<tr>
<td>TSHβ</td>
<td>Autosomal recessive</td>
<td>TSH deficiency</td>
</tr>
<tr>
<td>TTF-1 (TITF-1)</td>
<td>Autosomal dominant</td>
<td>Variable thyroid hypoplasia, choreoathetosis, pulmonary problems</td>
</tr>
<tr>
<td>TTF-2 (FOXE-1)</td>
<td>Autosomal recessive</td>
<td>Thyroid agenesis, choanal atresia, spiky hair</td>
</tr>
<tr>
<td>PAX-8</td>
<td>Autosomal dominant</td>
<td>Thyroid dysgenesis</td>
</tr>
<tr>
<td>TSH-receptor</td>
<td>Autosomal recessive</td>
<td>Resistance to TSH</td>
</tr>
<tr>
<td>Gsα (Albright hereditary osteodystrophy)</td>
<td>Autosomal dominant</td>
<td>Resistance to TSH</td>
</tr>
<tr>
<td>Na+/I- symporter</td>
<td>Autosomal recessive</td>
<td>Inability to transport iodide</td>
</tr>
<tr>
<td>DUOX2 (THOX2)</td>
<td>Autosomal dominant</td>
<td>Organization defect</td>
</tr>
<tr>
<td>DUOXA2</td>
<td>Autosomal recessive</td>
<td>Organization defect</td>
</tr>
<tr>
<td>Thyroid peroxidase</td>
<td>Autosomal recessive</td>
<td>Defective organization of iodide</td>
</tr>
<tr>
<td>Thyroglobulin</td>
<td>Autosomal recessive</td>
<td>Defective synthesis of thyroid hormone</td>
</tr>
<tr>
<td>Pendrin</td>
<td>Autosomal recessive</td>
<td>Pendred syndrome: sensorineural deafness and partial organization defect in thyroid</td>
</tr>
<tr>
<td>Dehalogenase 1</td>
<td>Autosomal recessive</td>
<td>Loss of iodide reutilization</td>
</tr>
</tbody>
</table>
Infant with only mild stigmata of congenital hypothyroidism

Athyrotic congenital hypothyroidism (sporadic)

Goitrous congenital hypothyroidism (endemic, sporadic, genetic)

Young child with marked stigmata of untreated congenital hypothyroidism

Elderly patient with untreated congenital hypothyroidism
Treatment

• Treatment of hypothyroidism
  • Causative
  • Thyroid hormone replacement - Levothyroxine
  • Iodine
    • Jod-Basedow effect (hyperthyroidism following administration of iodine or iodide)

• Screening
Levothyroxine treatment

• **TSH response** is gradual and should be measured about 2 months after starting treatment

• **Clinical effects** of levothyroxine replacement are slow to appear

• Patients may not experience **full relief** from symptoms until 3-6 months after normal TSH levels are restored
Guidelines for the Treatment of Hypothyroidism

Prepared by the American Thyroid Association
Task Force on Thyroid Hormone Replacement
Age ≤70

Serum TSH < 10

Hypothyroid symptoms?*

No

Observe and repeat TFT in 6 months

Yes

3-Month trial of LT₄, then assess response to treatment

Treat with LT₄

Age >70

Serum TSH < 10

Observe and repeat TFT in 6 months

Serum TSH ≥ 10

Consider LT₄ if clear symptoms of hypothyroidism or high vascular risk
Myxedema (coma)

- Rare, but deadly manifestation of severe hypothyroidism
- 60% mortality
- Hypothermia
- Hypotension and shock
- Hypoventilation
- Hypoglycemia
- Altered mental status / coma
Myxedema (coma)

- 90% of cases during winter
- Caused by altered temperature regulation in severely hypothyroid patient
- Almost never in patients younger than 60
- Physical findings – extreme hypothyroidism:
  - Dough-like non-pitting edema
  - Dry and brittle skin and hair
  - Delayed reflexes
  - Altered senses and mental state
Myxedema

• Increased deposition of connective tissue components
• Connective fibres are separated by an increased amount of protein and mucopolysaccharides that bind water
• Not fully understood
• 2 explanations
  • Fibroblast stimulation by TSH receptor (connective tissue cells react to high TSH levels)
  • Lymphocyte stimulation – Ab against TSH receptor in thyroid and connective tissue (Graves myxedema)
<table>
<thead>
<tr>
<th>Box 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Precipitating events causing myxedema coma</strong></td>
</tr>
<tr>
<td>Infection or sepsis</td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage</td>
</tr>
<tr>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Hypothermia</td>
</tr>
<tr>
<td>CO(_2) retention</td>
</tr>
<tr>
<td>Burns or trauma</td>
</tr>
<tr>
<td>Medications</td>
</tr>
<tr>
<td>Stroke</td>
</tr>
</tbody>
</table>

Features of hypothyroidism and hyperthyroidism

Hypothyroidism:
- Course and dry hair
- Dry skin
- Puffiness of the face
- Weight gain
- Swelling around the eyes
- Tiredness and lethargy
- Bradycardia
- Intolerant to cold

Hyperthyroidism:
- Lid retraction
- Anxious look
- Goitre
- Palpitations
- Intolerant to heat
- Weight loss
- Hand tremor
- Sweating