Hyperthyroidism
Hypothyroidism

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• Thureos (Greek) – oblong shield, door
• Thyroid gland – shield-shaped gland
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
• 1200 AD – sponges and seaweed for treatment of 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
Physiology

Thyroid system

- Hypothalamus
- Thyrotrpin-releasing hormone (TRH)
- Anterior pituitary gland
- Thyroid-stimulating hormone (TSH)
- Negative feedback
- Thyroid gland

- Thyroid hormones (T3 and T4)
- Increased metabolism
- Growth and development
- Increased catecholamine effect

Increased metabolism
Growth and development
Increased catecholamine effect

Hypothalamus

- Dopamine
- Somatostatin

Pituitary Gland

- TRH
- TSH

Thyroid Gland

- T3, T4

Peripheral Tissues

T3, T4
Iodine

- Iodide uptake is a critical first step in thyroid hormone synthesis
- 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
- **Thyroperoxidase** 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%)
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
Hyperthyroidism

- Definition
- Signs and symptoms
- Causes
- Diagnosis
- Treatment
Definition

• 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>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
<th>Differential Diagnosis</th>
</tr>
</thead>
<tbody>
<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>

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
<th>Differential Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck swelling</td>
<td>Goiter</td>
<td>Thyromegaly, infection</td>
</tr>
<tr>
<td>Eyelid swelling, redness, double vision</td>
<td>Proptosis, chemosis, conjunctival injection, lid lag</td>
<td>Ophthalmopathy, conjunctivitis, cellulitis</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Palpitations</td>
<td>Tachycardia, atrial fibrillation</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Dyspnea</td>
<td>Tachypnea</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Diarrhea, nausea, vomiting</td>
<td>Abdominal tenderness</td>
</tr>
<tr>
<td>Neuromuscular</td>
<td>Difficulty rising from chair, difficulty combing hair</td>
<td>Proximal muscle weakness</td>
</tr>
<tr>
<td>Extremity shaking</td>
<td>Tremor</td>
<td>Medication side effect, idiopathic</td>
</tr>
<tr>
<td>Skin</td>
<td>Discoloration</td>
<td>Thickening</td>
</tr>
<tr>
<td>Genitourinary/Endocrine</td>
<td>Amenorrhea, oligomenorrhea, Breast enlargement</td>
<td>Gynecomastia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Prevalence, %</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>

<table>
<thead>
<tr>
<th>Physical findings</th>
<th>Prevalence, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachycardia</td>
<td>80</td>
</tr>
<tr>
<td>Diffuse palpable goiter with an audible bruit</td>
<td>70</td>
</tr>
<tr>
<td>Increased pulse pressure</td>
<td>50</td>
</tr>
<tr>
<td>Tremor</td>
<td>40</td>
</tr>
<tr>
<td>Warm moist palms</td>
<td>35</td>
</tr>
<tr>
<td>Periorbital edema and proptosis</td>
<td>25</td>
</tr>
</tbody>
</table>
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 parenodular tissue and contralateral lobe</td>
<td>More common in older persons, women, and in areas of relative iodine deficiency</td>
</tr>
<tr>
<td>Painless thyroditis</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), usually positive anti-TPO antibodies</td>
<td>Absent to very low (0%-5%) 24-h RAI uptake, normal or decreased vascularity on Doppler-flow ultrasound</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 thyroditis</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 thyroditis</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 multikinase 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$_3$ with low FT$_4$ 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 choriocarcinoma</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**
Grave’s ophthalmopathy

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

Decreased $T_3$ and $T_4$ release

Cell necrosis

TRAb

Methimazole (12-18 mo)

RAI

Levothyroxine replacement

Methimazole (1-3 mo)

Levothyroxine replacement

Surgery
Aim: “To design synthetic biology-inspired gene circuit that can dynamically coordinate the therapeutic expression of a thyroid-stimulating hormone receptor-antagonist (TSH\textsubscript{Antag}) that can compete with endogeneous TSH or TSAb in the case of increased thyroid hormone levels, restore the feedback control mechanism along the hypothalamo-pituitary axis, and reset the homeostasis levels of thyroid hormones.”

Conclusion: Self-sufficient designer cells implants capable of maintaining thyroid homeostasis under disease conditions
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 hyperfunctional 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
Diffuse colloid goiter

Nodular goiter: variation in size and structure of nodules

Long-standing nodular goiter with hemorrhages, cyst formation, fibrosis, and calcification
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

European Thyroid Journal

Eur Thyroid J 2015;4:149–163
DOI: 10.1159/000438750

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

Bernadette Biondi³  Luigi Bartalena⁴  David S. Cooper⁵  Laszlo Hegedüs⁶  Peter Laurberg⁷  George J. Kahaly⁷
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>
<thead>
<tr>
<th>Signs</th>
<th>Symptoms</th>
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</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>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>

*Less common:
- Constipation (~ 50%)
- Hoarse voice (~ 40%)
- Menorrhagia (~ 30%)

*More common:
- Fatigue (~ 90%)
- Dry, scaly skin (~ 90%)
- Coarse, brittle thinning hair (~ 60%)
- Bradycardia (~ 40%)
- Hair loss or dryness (~ 70%)
- Anemia
- Puffy eyes (~ 90%)

*Less common:
- Constipation (~ 50%)
- Edema (~ 30%)
- Cerebellar signs*
- 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 – 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

Macroglossia, showing dental impressions

Central hypothyroidism (hypothalamic or pituitary origin)

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

Panhypopituitarism

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

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
Pathogenesis

• An autoimmune phenomenon – presentation determined by ratio of antibodies

Thyroid Stimulating Ab (TSAb)
Thyroid Stimulation Blocking Ab (TSBAb)
Thyroid peroxidase Ab (anti TPO)
Thyroglobulin Ab

Graves’ Disease
Autoimmune Hypothyroidism (Hashimoto’s)
Hashimoto thyroiditis

- Thyroid peroxidase and thyroglobulin
- Antigens
- Antibodies
- B cells in thyroid tissue and extrathyroidal lymphoid tissues
- Thyroid peroxidase and thyroglobulin antibody concentrations can be measured in serum

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, Autosomal dominant</td>
<td>Combined deficiencies of growth hormone, prolactin, thyroid-stimulating hormone (TSH)</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>G_{sa} (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>Organification defect</td>
</tr>
<tr>
<td>DUOXA2</td>
<td>Autosomal recessive</td>
<td>Organification defect</td>
</tr>
<tr>
<td>Thyroid peroxidase</td>
<td>Autosomal recessive</td>
<td>Defective organification 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 organisation defect in thyroid</td>
</tr>
<tr>
<td>Dehalogenase 1</td>
<td>Autosomal recessive</td>
<td>Loss of iodide reutilization</td>
</tr>
</tbody>
</table>
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
What to do to treat patients according to up-to-date knowledge?
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
<table>
<thead>
<tr>
<th>Box 2</th>
<th>Precipitating events causing myxedema coma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Infection or sepsis</td>
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<tr>
<td></td>
<td>Gastrointestinal hemorrhage</td>
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<td></td>
<td>Hypoglycemia</td>
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<td>Hypothermia</td>
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<td>CO₂ retention</td>
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<td>Burns or trauma</td>
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<td>Medications</td>
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<td>Stroke</td>
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</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
  - Weight loss
  - Intolerant to heat
  - Hand tremor