Hypothyroidism

Dr Piyush Tailor
Associate Professor
GMC, Surat
Introduction

- About 42 million people in India suffer from thyroid diseases.
- Prevalence of hypothyroidism = 3.9%
- More common in females.
- Second to DM, it is most common endocrine disorder.
Thyroid Regulation

HYPOTHALAMUS - TRH

ANT. PITUITARY - TSH

TSH - R

THYROID T4 and T3

PLASMA T4 + FT4

PLASMA T3 + FT3

TISSUES FT4 to FT3, rT3
Thyroid Hormone Synthesis

There are the following 5 steps in the hormonogenesis:

1. Trapping of inorganic Iodine from dietary Iodides
2. Activation of Iodine to high valance I$_2$
3. Incorporation of I$_2$ into Tyrosine of Thyroid Globulin
4. Coupling of formed MIT and DIT to form T$_4$ & T$_3$
5. Proteolysis of Thyroglobulin to release T$_4$ & T$_3$
Thyroid Hormone Biosynthesis

- Thyroid follicle
- Thyroglobulin
- Exocytosis
- Pendrin
- Thyroglobulin secretion
- Endoplasmic reticulum
- Nucleus
- Endothelium
- Blood
- I⁻
- Na⁺
- Na/I symporter
- Thyroxine
- Triiodothyronine
- MCT
- Oxidation
- I₀
- I⁻
# The Thyronines

<table>
<thead>
<tr>
<th>Thyronines</th>
<th>Acronym</th>
<th>Metabolic Activity</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mono Iodo Tyrosine (MIT)</td>
<td></td>
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<tr>
<td>Di Iodo Tyrosine (DIT)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Tri Iodo Thyronine (T&lt;sub&gt;3&lt;/sub&gt;)</td>
<td></td>
<td>Metabolically inactive</td>
<td>6 hours</td>
</tr>
<tr>
<td>Tetra Iodo Thyronine (T&lt;sub&gt;4&lt;/sub&gt;)</td>
<td></td>
<td>Metabolically inactive</td>
<td>7 days</td>
</tr>
<tr>
<td>Reverse T&lt;sub&gt;3&lt;/sub&gt;</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Bound hormones</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Free T&lt;sub&gt;4&lt;/sub&gt; and Free T&lt;sub&gt;3&lt;/sub&gt;</td>
<td></td>
<td>Metabolically Active</td>
<td></td>
</tr>
</tbody>
</table>
The Thyroxines

Tri Iodo Thyronine – $T_3$
- 10% is from thyroid gland
- 90% derived from conversion of $T_4$ to $T_3$

Tetra Iodo Thyronine – $T_4$
- Is exclusively from thyroid gland

From the thyroid gland
- 80% of hormone secreted is $T_4$
- 20% of hormone secreted is $T_3$
Classification of Hypothyroidism

Primary hypothyroidism (90%)
- high serum thyrotropin (TSH) concentration
- low serum free thyroxine (T4) concentration.

Secondary (central) hypothyroidism
- Low T4 concentration
- low TSH concentration

Subclinical hypothyroidism
- normal free T4 concentration
- elevated TSH concentration.
- Mild hypothyroidism, Preclinical hypothyroidism

Transient or temporary hypothyroidism
- can be observed as a phase of subacute thyroiditis.

Consumptive hypothyroidism
- Increase inactivation by 3 iodothyronine deiodinase (D3).
Type & Etiology of Hypothyroidism

- Primary hypothyroidism
- Secondary hypothyroidism
- Tertiary hypothyroidism
- Congenital hypothyroidism
- Autoimmune hypothyroidism
PRIMARY HYPOTHYROIDISM

- Idiopathic hypothyroidism
- Hashimoto’s thyroiditis
- Irradiation of thyroid
- Surgical removal
- Iodine deficiency
- Selenium deficiency
- Drug therapy induce
  - e.g. Amiodarone, Lithium, Interferon,
  - Long term Iodine excess (Wolff–Chaikoff effect)
- Infiltrative Diseases:
  - Amyloidosis
  - Hemochromatosis
SECONDARY HYPOTHYROIDISM
- Pituitary or hypothalamic neoplasm.
- Congenital hypopituitarism.
- Pituitary necrosis (Sheehan’s syndrome)

TERTIARY HYPOTHYROIDISM
- Hypothalamus related pathology

IATROGENIC HYPOTHYROIDISM
- After 3–4 months radioiodine treatment
- After Subtotal thyroidectomy

GOITROGENS
- DRUGS = Sulfonamides, Lithium, Oral Hypoglycemic drugs
- FOOD = Soybeans, Cabbage
CONGENITAL HYPOTHYROIDISM (CRETINISM)

- Infants appear normal at birth
- Delayed milestone
- Delayed bone maturation
- Permanent neurologic damage = if treatment is delayed
- Hypotonia
- Prolonged jaundice
- Feeding problems
- Umbilical hernia
- Enlarged tongue
- Congenital Cardiac malformations are 4 times more common.
Cretinism Face

- Dry & Thin Hair
- Short & Low nasal bridge
- Periorbital puffiness
- Large Head
- Short Forehead
- Big & Hypertrophy tongue
- Big Lips
AUTOIMMUNE HYPOTHYROIDISM

- Subclinical hypothyroidism
- Hashimoto's thyroiditis
- Anti TPO antibody & Anti TG antibody
- Lymphocytic infiltration of the thyroid
- Mild to moderate fibrosis.
- Atrophy of the thyroid follicles

Atrophic thyroiditis
- Fibrosis is much more extensive
- Represents end stage of Hashimoto's thyroiditis

Modifying Environmental Factor:
- Chronic exposure to high iodine diet
Associated conditions

- Other Autoimmune disorders: **(Most Common)**
  - Type 1 Diabetes mellitus
  - Addison's disease
  - Pernicious anemia
  - Vitiligo
  - Celiac disease
  - Rheumatoid Arthritis
  - Systemic Lupus Erythematos
CLINICAL MANIFESTATIONS

A generalized slowing of metabolic processes.
- Cold intolerance
- Constipation
- Weight gain
- Fatigue
- Slow movement
- Slow speech

Accumulation of Matrix Glycosaminoglycans (GAG)
- Myxedema
- Coarse hair and skin
- Puffy facies
- Enlargement of the tongue
- Hoarseness.
<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
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<tbody>
<tr>
<td>Decrease Appetite</td>
<td>Bradycardia</td>
</tr>
<tr>
<td>Cold Intolerance</td>
<td>Myxedema</td>
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<tr>
<td>Horseness of Voice</td>
<td>Goiter</td>
</tr>
<tr>
<td>Weight Gain</td>
<td>Depression</td>
</tr>
<tr>
<td>Eyelid edema</td>
<td>Facial edema</td>
</tr>
<tr>
<td>Constipation</td>
<td>Cold Skin</td>
</tr>
<tr>
<td>Forgetfulness</td>
<td>Dry &amp; Coarse skin</td>
</tr>
<tr>
<td>Slow speech</td>
<td>Pallor</td>
</tr>
<tr>
<td>Weakness</td>
<td></td>
</tr>
<tr>
<td>Decrease Sweating</td>
<td></td>
</tr>
</tbody>
</table>
CLINICAL MANIFESTATIONS

- **General**
  - Weight Gain
  - Goiter
  - Cold Intolerance
- **Skin & Subcutaneous issue**
  - Coarse & Dry Skin
  - Puffiness of face
  - Myxoedema
  - Minimum sweating
  - Alopecia
  - Non Pitting Edema
- **Cardiac**
  - Bradycardia
  - Cardiomyopathy
  - Cardiac Failure
  - Pericardial & Pleural effusion
- **Neuromuscular**
  - Carpal Tunnel Syndrome
  - Slurred speech
  - Horseness of voice
  - Ataxia
  - Muscle Cramp
  - Myopathy
- **Respiratory**
  - Shortness of Breath
  - Sleep apnea
- **Hematological**
  - Iron deficiency anemia
  - Perniciac anemia
CLINICAL MANIFESTATIONS

- **G.I.T.**
  - Constipation
  - Ascites

- **Reproductive System**
  - Menorrhagia
  - Infertility
  - Decrease Libido

- **Psychiatrics**
  - Depression
  - Dementia
  - Psychosis

- **Developmental**
  - Growth retardation
  - Delayed Puberty
  - Mental retardation

- **Metabolic**
  - Hyponatremia
  - Hypercholesterolemia
  - Hypertriglyceridemia

- **Miscellaneous**
  - Hoarseness of voice because of vocal cord thickening
  - Hyperlipidemia
  - Xanthomas
Laboratory Evaluation

**Thyroid Function Tests**
- Total T4 (thyroxine), Total T3 (triiodothyronine)
- Free T4, Free T3
- TSH
- Iodine Uptake Test
- Anti-Thyroid Antibodies
- Anti TPO Antibody
- FNAC of nodule
Thyroid Antibodies

- Anti Microsomal (TM) Antibodies
- Anti Thyroglobulin (TG) Antibodies
- Anti Thyroperoxidase (TPO) Antibodies
- Anti Thyroxine Antibodies
- Thyroid Stimulating (TSA) Antibodies

- High TPO Ab = Hashimoto’s thyroiditis
- High Anti thyroxine Ab = Peripheral resistance to Thyroxine
- High TSA (TSI) = Graves’ Hyperthyroidism
## Tests of Thyroid Function

<table>
<thead>
<tr>
<th>Test</th>
<th>Reference Ranges*</th>
</tr>
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<tbody>
<tr>
<td>TSH</td>
<td>0.3 - 4.0 mU/L</td>
</tr>
<tr>
<td>T4</td>
<td>4 - 11 μg/ dL</td>
</tr>
<tr>
<td>Free T4</td>
<td>0.7 - 2.1 ng/ dL</td>
</tr>
<tr>
<td>T3</td>
<td>75 - 175 ng/ dl</td>
</tr>
<tr>
<td>Free T3</td>
<td>0.300 - 0.7 ng / dl</td>
</tr>
</tbody>
</table>
Symptoms and signs suggesting hypothyroidism

Serum TSH and free T₄ or free T₄I

TSH increased
Free T₄ low or low normal

Primary hypothyroidism

TPO antibody

Present → Hashimoto's disease

Absent → ? Transient hypothyroidism? Postviral thyroiditis

T₄ ~4 months

Reduce T₄ by 50% for 6 weeks Check TSH

Normal thyroid

Increased

T₄

TSH normal or low
Free T₄ low or low normal
No phenytoin
No salicylates
No recent thyrotoxicosis

Central hypothyroidism

MRI

Abnormal → Pituitary or hypothalamic lesion

Check adrenal, prolactin, gonads

Normal → Congenital TRH, TSH deficiency
infiltrative disease of pituitary, hypothalamus

Treat with surgery or drugs after correction of adrenal, thyroid, other deficiencies
Treatment

- Treatment of choice is **Thyroxine**
- TSH measured = 6 to 8 weeks interval
- Adults = 1.7 microgm/kg/day (100 microgram/day)
- Elderly = 1.0 microgm/kg/day (50 - 75 microgram/day)
- Children may need up to 4 microgm/kg/day
- Increase in increments of 25 microgm every four weeks until TSH returns to normal.
- If Serum albumin low
  - Decrease dose by 20%.
Over - and Under- Dose Replacement Risks

- **Over-replacement Risks**
  - Reduced bone density/osteoporosis
  - Tachycardia, arrhythmia: Atrial fibrillation
  - In elderly or patients with heart disease, angina, arrhythmia, or myocardial infarction

- **Under-replacement Risks**
  - Continued hypothyroid state
  - Long-term end-organ effects of hypothyroidism
  - Increased risk of hyperlipidemia
Recovery after L-Thyroxine

Before

After
2010
After 2 years on Eltroxin (T4) only

2014
After 3 years on Eltroxin (T4) and T3