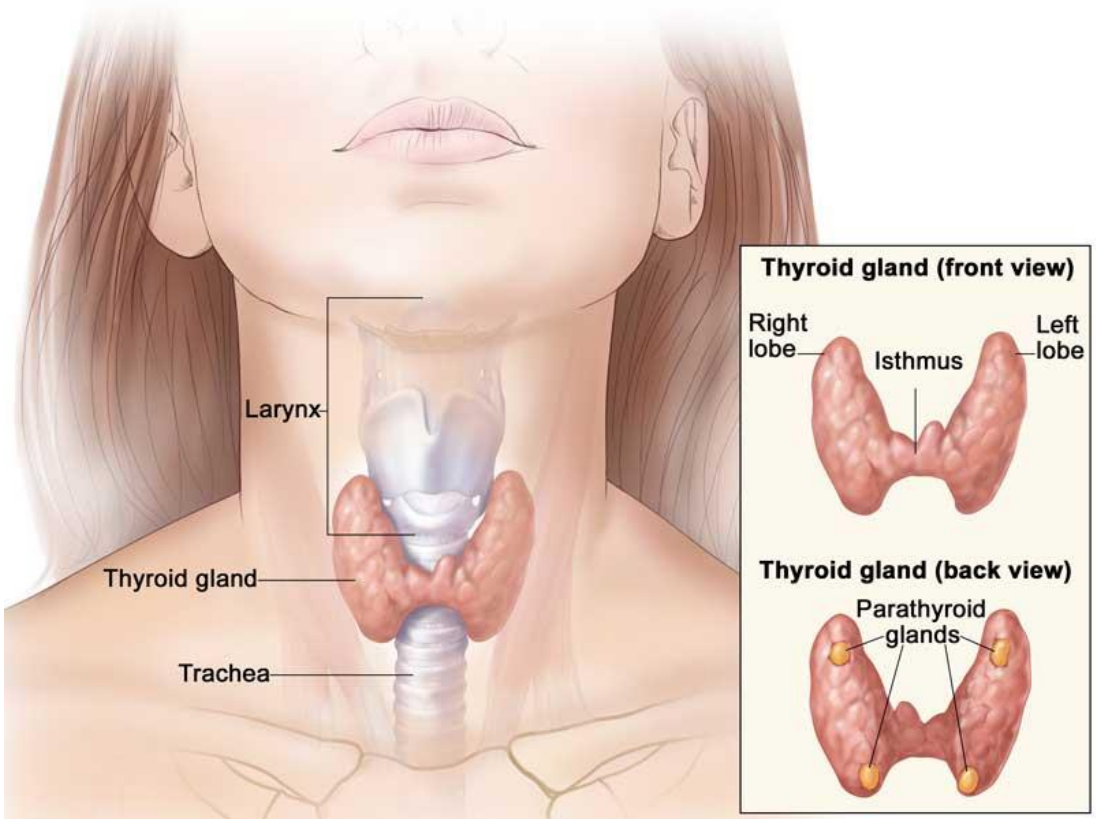
Hypothyroidism and Cretinism



Hypothyroidism

- The metabolism of virtually all nucleated cells of many tissues is controlled by the thyroid hormones.
- Thyroid abnormalities can be due ;
  - Epidemiological Abnormalities
  - **Functional Abnormalities**

    Hypothyroidism

    Hyperthyroidism
  - Morphological Abnormalities
- Hypothyroidism occurs due to primary or secondary causes.

Epidemiology

- Primary hypothyroidism is one of the most common endocrine conditions, with an overall UK prevalence of over 2% in women but under 0.1% in men.
- Life time prevalence for an individual is higher perhaps as high as 9% for women and 1% for men.
- The worldwide prevalence of subclinical hypothyroidism varies from 1% to 10%.

Etiology

- **Primary Hypothyroidism**

Congenital	Defects of hormone synthesis	Autoimmune	Infective
Agenesis	Iodine deficiency	Atropic thyroiditis	Post-subacute thyroiditis
	Dyshormonogenesis	Hashimoto's thyroiditis	
Ectopic thyroid remnants	Anti-thyroid drugs	Postpartum thyroiditis	
	Other drugs (e.g. lithium, amiodarone, interferon)		

Autoimmune causes

Atrophic (autoimmune) hypothyroidism

- Most common cause of hypothyroidism and is associated with anti-thyroid auto antibodies, leading to lymphoid infiltration of the gland and eventual atrophy and fibrosis.
- It is six times more common in females and the incidence increases with age.
- Associated with other autoimmune diseases, such as pernicious anaemia, vitiligo and other endocrine deficiencies.

Autoimmune causes

Hashimoto's thyroiditis

- More common in women and most common in late middle age.
- Produces atrophic changes with regeneration, leading to goitre formation.
- Thyroid peroxidase(TPO) antibodies are present, often in very high titres (>1000 IU/L).
- Patients may be hypothyroid or euthyroid, though they may go through an initial toxic phase, 'Hashi-toxicity'.
- Levothyroxine therapy may shrink the goitre, even when the patient is not hypothyroid.

Autoimmune causes

Postpartum thyroiditis

- This is usually a transient phenomenon observed following pregnancy.
- It may cause hyperthyroidism, hypothyroidism or the two sequentially.
- It is believed to result from the modifications to the immune system necessary in pregnancy.
- The process is normally self-limiting.
- But when conventional antibodies are found there is a high chance of this proceeding to permanent hypothyroidism.
- Postpartum thyroiditis may be misdiagnosed as postnatal depression, emphasizing the need for thyroid function tests in this situation.

Defects of hormone synthesis

Iodine deficiency

- Dietary iodine deficiency causes ‘endemic goitre’ in some areas.
- The patients may be euthyroid or hypothyroid, depending on the severity of iodine deficiency.
- Iodine deficiency is still a problem in the Netherlands, Western Pacific, India, South-east Asia,Russia and parts of Africa.
- Efforts to prevent deficiency by providing iodine in salt continue in worldwide.
- The recommended daily intake of iodine should be at least 140 µg.

Defects of hormone synthesis

Dyshormonogenesis

- This rare condition is due to genetic defects in the synthesis of thyroid hormones
- Patients develop hypothyroidism with goitre.
- Particular familial form is associated with sensorineural deafness due to a deletion mutation in chromosome 7 - **Pendred's syndrome**

Clinical Features

General
Tiredness
Weight gain
Cold intolerance
Goitre
Hyperlipidaemia
Dry thin hair
Loss of eyebrows

Cardiovascular
Bradycardia
Angina
Cardiac failure
Pericardial effusion
Anaemia

Skin
Dry skin
Vitiligo
Alopecia
Erythema

Gastrointestinal
Constipation

Other
Slow relaxing reflexers
Depression

Developmental
Growth and mental retardation
Delayed puberty

Reproductive
Infertility
Menorrhagia
Galactorrhoea
Poorlibido

Investigations

TSH	• High TSH level confirms primary hypothyroidism
T3, T4	• Low free T4 level confirms the hypothyroid state
TPO antibodies	• Elevated in Hashimoto's thyroiditis

Other Investigations

- **Full blood count** – anaemia; usually normochromic normocytic but may be macrocytic (due to associated pernicious anaemia) or microcytic (in women, due to menorrhagia or undiagnosed coeliac disease)
- **Liver function tests** - increased serum aspartate transferase levels, from muscle and/or liver
- **Serum creatine kinase** - increased levels, with associated myopathy
- **Lipid profile** - hypercholesterolaemia and hypertriglyceridaemia
- **Serum electrolytes** - hyponatraemia due to an increase in ADH and impaired free water clearance.

Management

Replacement therapy

- With levothyroxine (thyroxine, i.e. T4) is given for life.
- The starting dose will depend on
  - severity of the deficiency
  - age and fitness of the patient
  - cardiac performance

Young patients	• 100 µg
Small, old or frail patients	• Initially 50µg • Increasing to 100µg after 2 – 3 weeks
In ischemic heart disease	• Start with lower doses(25µg) • Perform serial ECGs and increasing dose in 3 to 4 week intervals if angina dose not worsen

Management

Monitoring

- The aim is to restore T4 and TSH to well within the normal range.
- Assessed clinically and by thyroid function tests after at least 6 weeks on a steady dose.
- If serum TSH remains high, the dose of T4 should be increased in increments of 25–50 µg, and the tests repeated at 6–8-weeks until TSH becomes normal, ideally in the lower third of the normal range

Management

- Complete suppression of TSH should be avoided because of the risk of atrial fibrillation and osteoporosis.
- The usual maintenance dose is 100–150 µg given as a single daily dose.
- An annual thyroid function test is recommended.
- Clinical improvement on T4 may not begin for 2 weeks or more, and full resolution of symptoms may take 6 months.

Management

- Possibility of developing other autoimmune endocrine disease, especially Addison's disease or pernicious anaemia, should be considered
- During pregnancy, an increase in T4 dosage of about 25–50 µg is often needed to maintain relatively stricter TSH range of 0.3–2.5 mU/L in order to prevent reductions in cognitive function in children

Borderline hypothyroidism or ‘compensated euthyroidism’

- Patients are frequently seen with low-normal serum T4 levels and slightly raised TSH levels.
- Treatment with levothyroxine is normally recommended where the TSH is consistently above 10 mU/L, or when possible symptoms, high-titre thyroid antibodies, or lipid abnormalities are present.
- Where the TSH is only marginally raised, the tests should be repeated 3–6 months later, as a significant proportion will be normal on repeat testing.

Myxoedema coma

- Severe hypothyroidism, especially in the elderly, may present with confusion or even coma.
- Most physicians would advise T3 orally or intravenously in doses of 2.5–5 µg every 8 hours, then increasing as above.
- Additional measures should include;
  - oxygen (by ventilation if necessary)
  - monitoring of cardiac output and pressures
  - gradual rewarming
  - hydrocortisone 100 mg i.v. 8-hourly
  - glucose infusion to prevent hypoglycaemia

Myxoedema madness

- Depression is common in hypothyroidism.
- Rarely, with severe hypothyroidism in the elderly, the patient may become frankly demented or psychotic, sometimes with striking delusions.
- This may occur shortly after starting T4 replacement.

Congenital hypothyrodism

- The incidence of congenital hypothyroidism *is* approximately 1 in 3500 births.
- Untreated, severe hypothyroidism produces permanent neurological and intellectual damage **'Cretinism'**
- It is a preventable cause of severe learning difficulties.

Etiology

Maldescent of the thyroid and athrosis	• Most common cause of sporadic congenital hypothyroidism • In maldescent, the thyroid remains as a lingual mass or a unilobular small gland
Dyshormogenesis	• Inborn error of thyroid hormone synthesis • About 5% to 10% of cases • More common in some ethnic groups with consanguineous marriage
Iodine deficiency	• The most common cause of congenital hypothyroidism worldwide but rare in UK • Can be prevented by iodination of salt in the diet

Etiology

TSH deficiency

- Isolated TSH deficiency is rare (<1% of cases)
- Usually associated with pituitary dysfunction and manifestation of other pituitary hormone deficiencies which appears earlier

Clinical features

- Growth faltering
- Feeding problems
- Prolonged jaundice
- Constipation
- Pale, cold, mottled dry skin
- Coarse facies
- Large tongue
- Hoarse cry
- Goitre (occasionally)
- Umbilical hernia
- Delayed development

Investigations

- Detected on routine neonatal biochemical screening **'Guthrie test'** performed on all newborn infants, by identifying a raised TSH in the blood.
- Thyroid dysfunction secondary to pituitary abnormalities will not be picked up at neonatal screening as they have a low TSH.
- In some countries T4 is also measured.

Management

- Treatment with thyroxine should be started before 2 weeks to 3 weeks of age to reduce the risk of impaired neurodevelopment
- Treatment is lifelong with oral replacement of thyroxine, titrating the dose to maintain normal growth, TSH and T4 levels