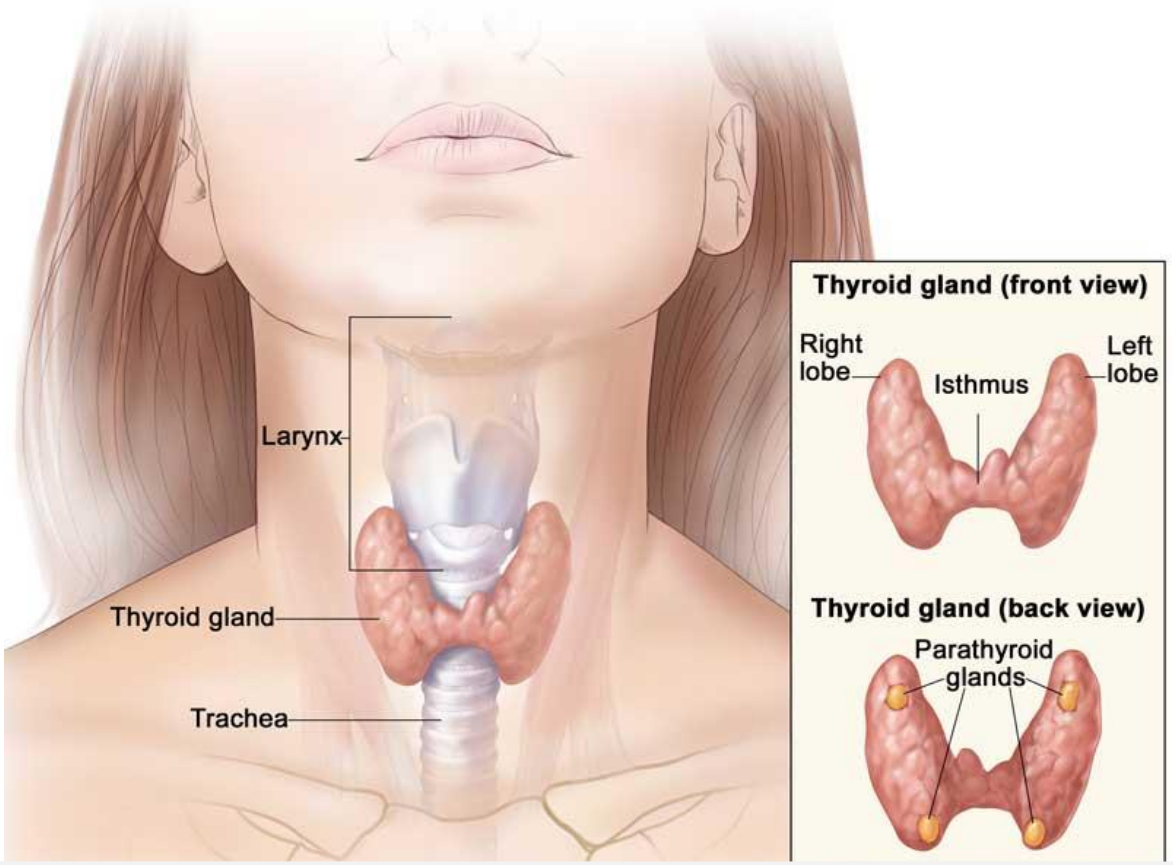
# Hyperthyroidism



# Hyperthyroidism

- 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**
    - **Hyperthyroidism**
    - Hypothyroidism
  - –Morphological abnormalities

# Epidemiology

- Hyperthyroidism (thyroid overactivity, thyrotoxicosis) is common, affecting perhaps 2–5% of all females
- Female to male ratio is 5 : 1
- Most often occurs between the ages of 20 and 40 years
- Nearly all cases (>99%) are caused by intrinsic thyroid disease
- A pituitary cause is extremely rare

# Etiology

**Common**
- Graves' disease (autoimmune)
- Toxic multinodular goitre
- Solitary toxic nodule/adenoma

**Rare**
- TSH-secreting pituitary tumours
- Metastatic differentiated thyroid carcinoma
- HCG-producing tumours
- Hyperfunctioning ovarian teratoma (struma ovarii)

**Uncommon**
- Acute thyroiditis
  - Viral (e.g. de Quervain's)
  - Autoimmune
  - Post-irradiation
  - Postpartum
- Gestational thyrotoxicosis (HCG-stimulated)
- Neonatal thyrotoxicosis (maternal thyroid antibodies)
- Exogenous iodine
- Drugs –
  Amiodarone
  Immunotherapy (ipilimumab, pembrolizumab, Nivolumab)
- Thyrotoxicosis factitia (secret T4 consumption)

# Hyperthyroidism

## Primary

- Symptoms appear first or with the goitre
- Occurs in Graves' disease
- Common in young
- Eye signs are common

## Secondary

- Thyroid swelling appears first- Toxic features appear later
- Occurs in multinodular goitre
- Common in old age group
- Eye signs are not common
- Cardiac features are common- Tachycardia, Ectopics, Atrial tachycardia, Atrial fibrillation

# Clinical Features

## Symptoms

Thirst
Vomiting
Diarrhoea

Oligomenorrhoea
Loss of libido
Gynaecomastia

Onycholysis
Goiter

**General**
Weight loss
Irritability
Restlessness
Malaise
Itching
Sweating
Tall stature (in children)
Breathlessness
Palpitation
**Heat intolerance**
Stiffness
Muscle weakness
Tremor
Choreoathetosis

# Clinical Features

## Signs

**Tremor**
**Hyperkinesis**
Psychosis

Proximal myopathy
Proximal muscle wasting
Onycholysis
Palmer erythema

Graves dermopathy
Thyroid acropachy
Pretibial myxoedema

**Exopthalmus**
**Lid lag**
Conjunctival oedema
Opthalmoplegia
Periorbital oedema
**Goiter, bruit**
Weight loss

**Tachycardia or atrial fibrillation**
**Full pulse**
**Warm peripheries**
Systolic hypertention
Cardiac failure

# Graves' disease

- This is the most common cause of hyperthyroidism and is due to an autoimmune process
- A diffuse vascular goitre appearing at the same time as hyperthyroidism
- Usually occurs in younger women and is frequently associated with eye signs
- The syndrome is that of primary thyrotoxicosis
- 50% of patients have a family history of autoimmune endocrine diseases such as pernicious anaemia, vitiligo and myasthenia gravis

# Graves' disease

**Pathophysiology**

- Serum IgG antibodies bind to TSH receptors in the thyroid, stimulating thyroid hormone production as they behave like TSH
- These **TSH receptor antibodies (TSHR-Ab) are specific for Graves' disease**
- *Yersinia enterocolitica, Escherichia coli and other Gram negative* organisms contain TSH-binding sites. This raises the possibility that the initiating event in the pathogenesis

# Toxic nodular goitre

- A simple nodular goitre is present for a long time before the Hyperthyroidism
- Usually in the middle-aged or elderly
- Very infrequently is associated with eye signs
- The syndrome is that of secondary thyrotoxicosis

# Toxic nodular goitre

**Pathophysiology**

- In many cases of toxic nodular goitre, the nodules are inactive, and it is the internodular thyroid tissue that is overactive
- In some toxic nodular goitres, one or more nodules are overactive
- Here the hyperthyroidism is due to autonomous thyroid tissue as in a toxic adenoma

# Solitary Toxic nodule

- A toxic nodule is a solitary overactive nodule, which may be part of a generalised nodularity or a true toxic adenoma
- This is the cause of about 5% of cases of hyperthyroidism
- While the hyperthyroidism will be controlled by the anti-thyroid drugs, it does not usually remit after a course of anti-thyroid drugs

# Solitary Toxic nodule

**Pathophysiology**

- It is autonomous and its hypertrophy and hyperplasia are not due to TSH-Rab
- TSH secretion is suppressed by the high level of circulating thyroid hormones
- The normal thyroid tissue surrounding the nodule is itself suppressed and inactive

# De Quervain's thyroiditis

- This is transient hyperthyroidism from an acute inflammatory process, probably viral in origin

**Clinical features**

- Thyrotoxicosis
- Fever
- Malaise
- pain in the neck
- tachycardia
- local thyroid tenderness

# De Quervain's thyroiditis

- Thyroid function tests show initial hyperthyroidism
- Erythrocyte sedimentation rate (ESR) and plasma viscosity are raised
- Thyroid uptake scans show suppression of uptake in the acute phase
- Hypothyroidism, usually transient, may then follow after a few weeks
- Treatment of the acute phase is with **aspirin**, using short-term **prednisolone** in severely symptomatic cases

# Amiodarone-induced thyrotoxicosis

- Amiodarone, a class III antiarrhythmic drug, causes two types of hyperthyroidism.

**Type I amiodarone-induced thyrotoxicosis (AIT)**

- Associated with pre-existing Graves' disease or multinodular goitre
- In this situation, hyperthyroidism is probably triggered by the high iodine content of amiodarone

**Type II amiodarone-induced thyrotoxicosis**

- Not associated with previous thyroid disease
- Due to a direct effect of the drug on thyroid follicular cells, leading to a destructive thyroiditis with release of T4 and T3
- may be associated with a hypothyroid phase several months after presentation
- Because amiodarone inhibits the deiodination of T4 to T3

- Biochemical presentation of both types of AIT may be associated with higher T4 : T3 ratios than usual

# Immunotherapy-induced thyrotoxicosis

- Cancer immunotherapy drugs that block negative regulators on T cells
- These drugs cause immune-related adverse events (irAEs) in various organs, including in endocrine glands
- Thyroiditis is the most common of endocrine irAEs and occurs between 3 and 12 weeks after initiation of the drug
- Treatment is with **beta-blockers**, **analgesia** and, rarely, with **anti-thyroid medication** if thyrotoxicosis persists, especially with symptoms

# Investigations

| | |
|---|---|
| TSH | • Serum TSH is suppressed in hyperthyroidism (<0.05 mU/L) except for the very rare instances of TSH hypersecretion |
| T3,T4 | • A raised free T4 or T3 confirms the diagnosis<br>• T4 is almost always raised<br>• T3 is more sensitive<br>• There are occasional cases of isolated ‘T3 toxicosis |
| TSH receptor stimulating antiodies | • Now measured routinely<br>• The third-generation tests are 97–99% specific for Graves’ disease |

# Investigations

| | |
|---|---|
| Thyroid peroxidase and Thyroglobulin antiodies | • Are present in 80% of cases of Graves' disease<br>• But are also found in normal individuals |
| Scintiscan 99Tm | • Is used in patients who are antibody negative to look for toxic nodular disease |

# Management

- Three possibilities are available;
  - Anti-thyroid drugs
  - Radio-iodine
  - Surgery
- Practices and beliefs differ widely within and between countries

# Management

- Carbimazole is most often used in the UK, and propylthiouracil (PTU) is also an option
- Thiamazole (methimazole), the active metabolite of carbimazole, is used in the USA
- These drugs inhibit the formation of thyroid hormones

# Management

- Beta-blockers are used to provide rapid partial symptomatic control; they also decrease peripheral conversion of T4 to T3 (Propranolol)
- They should not be used alone for hyperthyroidism except when the condition is self-limiting, as in subacute thyroiditis
- Subsequent management is either by gradual dose titration or by a ‘block and replace’ regimen
- Neither regimen has been shown to be unequivocally superior

# Management

| | |
|---|---|
| **Carbimazole** | • 20–40 mg daily, 8-hourly or in Single dose |
| **Propylthiouracil** | • 100–200 mg, 8-hourly |
| **Propranolol** | • 40–80 mg, every 6–8 h |

# Gradual dose titration

1

- Start carbimazole 20–40 mg daily

2

- Review after 4–6 weeks and reduce the dose of carbimazole, depending on clinical state and fT4/fT3 levels
- TSH levels may remain suppressed for several months and are unhelpful at this stage

3

- When the patient is clinically and biochemically euthyroid, stop beta-blockers

# Gradual dose titration

4

- Review thyroid function regularly during the planned course of treatment
- Typically 18 months – but some use courses between 6 and 24 months

5

- Reduce carbimazole if fT4 falls below or TSH rises above normal, and when approaching the end of the planned course

6

- Increase carbimazole if fT4 or fT3 is above

7

- Stop treatment at the end of the course if the patient is euthyroid on 5 mg daily carbimazole

# Block and replace' regimen

- With this policy, full doses of anti-thyroid drugs, usually carbimazole 40 mg daily, are given to suppress the thyroid completely while replacing thyroid activity with 100 µg of levothyroxine daily once euthyroidism has been achieved
- This is continued usually for 18 months
- This regimen is contraindicated in pregnancy, as T4 crosses the placenta less well than carbimazole

# Relapse

- About 50% of patients will relapse after a course of carbimazole or PTU, mostly within the following 2 years
- Long-term anti-thyroid therapy is then used, or surgery or radiotherapy is considered

# Toxicity

- The major side-effect of drug therapy is agranulocytosis, which occurs in approximately 1 in 1000 patients, usually within 3 months of treatment
- All patients must be warned to seek immediate medical attention and to have a check of their white blood cell count if they develop unexplained fever or sore throat
- Rashes are more frequent and usually require a change of drug
- If toxicity occurs on carbimazole, PTU may be used

# Radioactive iodine

- Radioactive iodine (RAI) is given to patients of all ages, although it is contraindicated in pregnancy and while breast-feeding
- 131Iodine is given in an empirical dose (usually 400–550 MBq)
- It accumulates in the thyroid and destroys the gland by local radiation, although it takes several months to be fully effective
- Patients must be rendered euthyroid before start treatment

# Surgery

- Thyroidectomy should be performed only in patients who have previously been rendered euthyroid
- Conventional practice is to stop the anti-thyroid drug 10–14 days before operation
- Then give potassium iodide (60 mg three times daily), which reduces the vascularity of the gland and reduces thyroid hormone synthesis by inhibiting organification of iodine (Wolff–Chaikoff effect)

# Thyroid Crisis

- Thyroid crisis or ‘thyroid storm’ is rare condition, with a mortality of 10%
- Rapid deterioration of hyperthyroidism with hyperpyrexia, severe tachycardia, extreme restlessness, cardiac failure and liver dysfunction.
- It is usually precipitated by stress, infection or surgery in an unprepared patient, or by radio-iodine therapy

# Thyroid Crisis

- Treatment is urgent
- This requires ;
  - administration of intravenous fluids
  - cooling the patient with ice packs
  - administration of oxygen
  - diuretics for cardiac failure
  - Digoxin for uncontrolled atrial fibrillation
  - sedation
  - intravenous hydrocortisone
- Specific treatment is by;
  - Carbimazole 10–20 mg 6-hourly
  - Lugol's iodine 10 drops 8-hourly by mouth or sodium iodide 1g
  - IV Propranolol intravenously (1–2 mg) or orally (40 mg 6-hourly) will block β-adrenergic effects