1. Hyposecretion of Anterior Pituitary Hormones

Professor John Laycock

The hypothalamo-adenohypophysial axis comprises the hypothalamus, anterior pituitary and various endocrine glands. The hypothalamus is made up of neurones, some of which terminate on the region of median eminence + some of which terminate within the APG. These secrete hormones, which stimulate or inhibit the release of hormones from the anterior pituitary into the general circulation. Anterior pituitary hormones then have their effects on the body and on endocrine glands which may be stimulated to release primary hormones.

- Disorder at the endocrine gland results in primary endocrine gland disease
- Disorder at the anterior pituitary results in secondary endocrine gland disease
- Disorder at the hypothalamus results in tertiary endocrine gland disease

**HYPOPITUITARISM**

“Hypopituitarism is the decreased production of all anterior pituitary hormones or the decreased production of specific hormones”

**Panhypopituitarism** is the decreased production of all anterior pituitary hormones. It is a rare case caused by congenital defects or gene mutations in the genes involved in the development of the gland (e.g. PROP1). It can also occur after radiotherapy.

In adults, it presents as the progressive loss of pituitary secretion, often (but not invariable) in the following order (reflected distribution of the cells within the gland):

- Gonadotrophins (LH and FSH)
- GH
- Thyrotrophin
- Corticotrophin
- (Prolactin deficiency is uncommon)

There are various causes of panhypopituitarism:

**Simmonds’ disease** is insidious (slow) in onset, caused by various things including infiltrative processes (e.g. lymphocytic), pituitary adenomas, craniopharyngiomas, cranial injury and following surgery.

- Symptoms are due mainly to decreased thyroidal, adrenal and gonadal function. The result is secondary amenorrhoea or Oligomenorrhoea (women), impotence (men), loss of libido, tiredness, waxy skin, loss of body hair, hypotension, etc.
- Diagnosis of hypopituitarism is made using basal plasma values of pituitary or target endocrine gland hormones. These are particularly useful if measured after a stimulation or ‘provocation’ test, for example using a combined function test involving rapid iv sequential administration of GHRH, CRH, GnRH and TRH. For individual hormones, more specific tests can be used e.g. insulin-induced hypoglycaemia for GH.

**Sheehan’s syndrome** is hypopituitarism specific in women. It develops acutely following post-partum haemorrhage, whereby blood loss + hypovolaemic shock causes vasoconstrictor spasm of the hypophysial arteries, leading to ischaemia and subsequent necrosis of the pituitary gland (this is not helped by the fact that the APG is enlarged during pregnancy, therefore requires a larger blood supply)

**Pituitary apoplexy** is a similar intra-pituitary haemorrhage in the presence of a pituitary adenoma. It often has dramatic presentation with pre-existing pituitary tumours which suddenly infarct. Many patients can be treated with supportive treatment alone. In some cases surgical decompression can be necessary although indications for intervention are controversial.
**Single adenohypophysial hormone deficiency**

NB: It is possible to have a deficiency in a single adenohypophysial hormone, resulting in secondary endocrine gland failure. For example...

- lack of **gonadotrophins** leading to hypogonadism
- lack of **thyrotrophins** leading to hypothyroidism
- lack of **corticotrophin** leading to hypoadrenocorticalism (loss of glucocorticoids – mineralocorticoid production is not affected by lack of corticotrophin)

**Somatotrophin deficiency > Hypopituitary Dwarfism**

Lack of somatrophin (GH) in children results in pituitary dwarfism or short stature. In adults, the effect of the loss of GH is uncertain because by that point most of the growing is complete.

Causes of short stature include: Genetic determination; Malnutrition; Emotional deprivation; Endocrine disorders; and other various causes which are often unknown.

*In children...*

GH deficiency can be congenital, but this is rare. It can be due to...

- Deficiency of hypothalamic GHRH
- Mutations of the GH gene (very rare)
- Developmental abnormalities (e.g. aplasia or hypoplasia of the pituitary)

Acquired deficient is more common and can be due to...

- Tumours of the hypothalamus or pituitary
- Other intracranial tumours nearby (e.g. optic nerve glioma)
- Secondary to cranial irradiation (radiotherapy)
- Head injury
- Infection or inflammation
- Severe psychological deprivation

**Other endocrine-related causes of short stature**

It must be remembered that the hormone can only work if the receptor + post-receptor mechanisms are working, so short stature is not always a disorder of hormone production...

*Laron dwarfism* – caused by GH receptor defect in the intracellular mechanism complex of the hepatocytes

- Remember, the liver is also a relevant organ. Somatotrophin binds with a GH receptor on hepatocytes, stimulating insulin growth factors I + II (IGF1 + IGF2)
- IGF1 has a similar effect to somatotrophin on target tissues

*PYGMY* – caused by an IGF1 receptor defect on the target tissues

**Tertiary hypopituitarism** involves specific hypothalamic hormone defects. These include...

*Kallmann’s Syndrome* – caused by a deficiency of GnRH; leads to a decreased functioning of the glands that produce sex hormones

*Prader-Willi Syndrome* – a rare genetic disorder in which seven genes on chromosome 15 are deleted/unexpressed on the paternal chromosome; one symptom manifests as hypogonadism.

**DIAGNOSIS**

To diagnose pituitary deficiency, a **provocative challenge (i.e. stimulation) test** is done.

- A **preliminary diagnosis** may be made on the bases of the signs and symptoms the patient presents with. However, a definitive diagnosis requires biochemical measurement of the hormone concerned.
- Since hormones are secreted periodically (often circadian rhythm) and the normal range may be broad, tests for pituitary insufficiency normally involve measurement of circulating hormone levels before and after a provocative challenge.
For example, growth hormone (GH) insufficiency may be diagnosed by measuring plasma GH before and after one of the following:

- GHRH (iv)
- Insulin (iv induced hypoglycaemia induces GH release; most common but is dangerous as inducing hypoglycaemic state)
- Arginine (iv)
- Exercise (e.g. 10 minute step climbing)

E.g. **insulin-induced growth hormone secretion**: the graph opposite shows the typical GH responses to insulin in a normal subject and one with a partial GH deficiency. NB: the time window needed to see the GH level response to administration of insulin is 2 hours.

**TREATMENT**
The principle aim of the treatment of pituitary deficiency is to **restore homeostasis** by replacing missing hormones. An accurate diagnosis is therefore critical.

**Hormone Replacement Therapy**
- ACTH, TSH and LH/FSH (pituitary hormones) largely produce their biological actions through stimulating the production of further hormones by the adrenal cortex, thyroid + gonads respectively.
- These second hormones are easier to administer than pituitary hormones, therefore a used in preference in replacement therapy.

<table>
<thead>
<tr>
<th>Deficient pituitary hormone</th>
<th>Diagnosis (check)</th>
<th>Replacement therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH</td>
<td>Serum cortisol</td>
<td>Hydrocortisone</td>
</tr>
<tr>
<td>TSH</td>
<td>Serum T&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Thyroxine</td>
</tr>
<tr>
<td>LH/FSH (in women)</td>
<td>Oestrogen deficiency (+ Libido)</td>
<td>Ethinyloestradiol/Medroxyprogesterone</td>
</tr>
<tr>
<td>LH/FSH (in men)</td>
<td>Serum testosterone (+ Libido)</td>
<td>Testosterone undecanoate</td>
</tr>
<tr>
<td>GH</td>
<td>IGF1 + growth chart</td>
<td>GH</td>
</tr>
</tbody>
</table>

**Growth Hormone Therapy**

In children accelerates linear growth and decreases body fat(stimulates protein synthesis + decreased fat storage). The effects are most marked in the first year of treatment, with younger children and obese children responding better. However, resistance may develop (antibody formation), and if the GH deficiency is associated with a more generalised hypopituitarism, replacement therapy with other hormones will be required.

- The **preparation** is human recombinant GH (approved name “somatotrophin”)
- The **administration** is a subcutaneous or intramuscular injection given daily, or 4-5 times per week. The dose is then adjusted to the patient’s size.
- The **absorption and distribution** gives a maximal plasma concentration in 2-6 hours.
- **Metabolism** is hepatic or renal, and the half-life is short (approx. 20 minutes)
- The **duration of action** lasts well beyond plasma clearance, with peak IGF1 levels at approximately 20 hours.
- The adverse effects include lipoatrophy at injection side, intracranial hypertension, headaches, increased incidence of leukaemia

In adults, growth hormone deficiency presents with various signs and symptoms...

- Reduced lean mass, increased adiposity + increased waist to hip ratio
- Reduced muscle strength + bulk, reduced exercise performance
- Decreased plasma HDL-cholesterol + raised LDL-cholesterol
- Impaired psychological well-being + quality of life

GH production tends to decrease in people over 60. A diagnosis is made by a lack of response to GH stimulation test (e.g. to insulin), low plasma IGF-1 and low plasma IGF-BP3.
• The potential benefits of GH therapy in adults include improved body composition, improved muscle strength + exercise capacity, normalisation of HDL-cholesterol, increased bone mineral content, improved psychological well-being and improved quality of life

• The potential risks of GH therapy in adults include increased risk of cardiovascular accidents, increased soft tissue growth (leading to e.g. cardiomegaly) and increased susceptibility to cancer
2. Hypersecretion of Anterior Pituitary Hormones

Professor John Laycock

Hyperpituitarism is usually due to isolated pituitary tumours but can also be ectopic (i.e. from non-endocrine tissue) in origin. It can quite often be associated with visual field and other (e.g. cranial nerve) defect. It can be detected through the symptoms associated with excess production of adenohypophysial hormones.

Bitemporal (heteronymous) hemianopia occurs when growth of a suprasellar tumour presses onto the optic chiasm, causing a lesion which damages the optic nerves. This leads to disruption of temporal visual paths, i.e. loss of peripheral vision.

The excess of various pituitary hormones can result in a number of different scenarios:

- **Excess corticotrophin** (ACTH) > Cushing’s disease
- **Excess thyrotrophin** (TSH) > thyrotoxicosis
- **Excess gonadotrophins** (LH/FSH) > precocious puberty in children (this is difficult to identify)
- **Excess prolactin** > hyperprolactinaemia
- **Excess somatotrophin** (GH) > Gigantism, Acromegaly

Hyperprolactinaemia is caused by excess circulating prolactin when not due to a physiological cause such as pregnancy or breast feeding, usually due to a prolactinoma (often microadenomas less than 10mm in diameter).

<table>
<thead>
<tr>
<th>In <strong>women</strong>, this results in...</th>
<th><strong>In men</strong>, this results in...</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galactorrhoea (milk production)</td>
<td>Galactorrhoea (uncommon since appropriate steroid background usually inadequate)</td>
</tr>
<tr>
<td>Secondary amenorrhoea or oligomenorrhoea</td>
<td>Loss of libido</td>
</tr>
<tr>
<td>Loss of libido</td>
<td>Impotence</td>
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<tr>
<td>Infertility</td>
<td>Infertility</td>
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</tbody>
</table>

**EXCESS SOMATOTROPHIN**

In childhoood, excess growth hormone results in gigantism. In adults, it results in acromegaly. Acromegaly is insidious in onset, with signs and symptoms progressing gradually over many years (can remain undiagnosed for 15-20 years)

- If untreated, gigantism and acromegaly are associated with an increased morbidity and mortality due to cardiovascular and/or respiratory complications
- Acromegaly involves increased **growth** of periosteal bone, cartilage, fibrous tissue, connective tissue, and internal organs (cardiomegaly, splenomegaly, hepatomegaly etc)
- The **metabolic effects** include an increased plasma insulin response to oral glucose load, which leads to increased insulin resistance, which results in an impaired glucose tolerance test in 50% of patients and diabetes mellitus in 10%
- Common clinical manifestations include:
  - Enlargement of supraorbital ridges and nose, hands + feet, thickening of lips and general coarseness of features
  - Excessive sweating (hyperhidrosis)
  - Mandible growth (leading to protrusion of lower jaw aka prognathism)
  - Carpal tunnel syndrome (in wrist) + joint pain
  - Barrel chest and curvature of spine (kyphosis)
  - Galactorrhoea (women + rarely in men), menstrual abnormalities, decreased libido + impotence
  - Hypertension
  - Abnormal glucose tolerance + symptoms of diabetes mellitus
**DIAGNOSIS + TREATMENT**

**Diagnosis** of pituitary hypersecretory states uses **suppression tests**.

- As for pituitary underactivity, preliminary diagnosis may be made on the basis of the signs and symptoms the patient presents with. However, a definitive diagnosis requires **biochemical measurements of the hormone concerned**.
- Since hormones are secreted episodically and the normal range is broad, tests for pituitary overactivity normally involve measurement of circulating hormone levels before and after treatment with an agent which normally causes **suppression of hormone release**.
- For example, acromegaly may be diagnosed by measuring plasma GH before and after an oral glucose load (shown in diagram opposite)

**Treatment** options for acromegaly are variable, but can be divided into 3 options: surgery; radiotherapy; and chemotherapy.
- Chemotherapy includes somatostatin analogues (e.g. octreotide) and dopamine agonists (e.g. bromocriptine).
- Surgery is transphenoidal (goes in through the nose)

**Octreotide** is a somatostatin analogue which may be used as a short-term treatment before pituitary surgery, or a long-term treatment in patients not controlled by other means.
- As it inhibits GH release, it can also be used to treat other neuroendocrine tumours e.g. carcinoid tumours
- It is **administered** subcutaneously or intramuscularly 3 times per day, with a depot preparation once GH levels are under control. The dose is adjusted according to need (unlike somatotrophin, where it is adjusted for patient’s size)
- It is **distributed** by being retained in the extracellular fluid, and its **metabolism** is renal or hepatic, with a half-life of 2-4 hours.
- **Unwanted side effects** include GI tract disturbances, transient hyperglycaemia (caused by an initial reduction in insulin secretion), and in rare cases gallstones

**NB:** *Hyperprolactinaemia* is treated using dopamine receptor agonists to decrease prolactin (and GH) secretion, and to reduce pituitary tumour sizes. Examples of these include bromocriptine and cabergoline.

**Bromocriptine** is a D$_2$ agonist, which is administered by mouth once daily.
- It is highly plasma protein bound (93%) and has a half-life of ~7 hours (following hepatic metabolism)
- Unwanted side effects of bromocriptine include:
  - Nausea, vomiting, abdominal cramps
  - Dyskinesias
  - Psychomotor excitation
  - Postural hypotension
  - Vasospasm in fingers and toes (caution Raynaud’s disease)
- Other uses of bromocriptine include suppression of lactation, cyclical benign breast pain/tumour treatment, acromegaly and Parkinson’s disease

**Cabergoline** is a D$_2$ receptor agonist (like bromocriptine) with moderate D$_1$ receptor activity. It is longer lasting than bromocriptine, taken orally once or twice per week and has a half-life of >45 hours. The unwanted effects are similar to that of bromocriptine, but less pronounced therefore is the drug of choice.
3. Neurohypophysial Disorders
Professor John Laycock

(See neurohypophysis notes from Endo Year 1) In the hypothalamo-neurohypophysial system, secretions are released into the general circulation. The supraptic and paraventricular nuclei (cell bodies) are located in the hypothalamus, and the axons pass through the median eminence through to the capillary network. The neurohypophysis secretes vasopressin and oxytocin.

The principle action of vasopressin is the antidiuretic effect. It acts on the V2 receptors of renal and cortical medullary collecting ducts, where it stimulates the synthesis and insertion of aquaporin 2 into the apical membranes of the principle cells. Aquaporin 2 than acts to increase water transport (reabsorption) from the tubular fluid into the general circulation, thus increasing the amount of water retained in the body.

The other actions of vasopressin are determined by its interaction with its different receptors:

- V1a receptors are responsible for the potent vasoconstrictor actions
- V1b receptors are found specifically on corticotrophs in the APG, and mediate the release of corticotrophin (ACTH)
- V2 receptors are involved in the production of Factor VIII + von Willebrand factor, therefor has an important role in blood clotting
- There is currently ongoing research into the central effects of vasopressin, including treatment for conditions to do with social behaviour such as autism.

The principle actions of oxytocin include constriction of myometrium at parturition, and also the milk ejection reflex. There may also be central effects. In high amounts of vasopressin and oxytocin there is overlap of pharmacological conditions and actions.

**LACK OF NEUROHYPOPHYSIAL HORMONES**

**Oxytocin** - parturition and milk ejection effects induced/replaced by other means.

**Vasopressin** - DIABETES INSIPIDUS

Diabetes notes that the amount of urine being produced is large. Unlike diabetes mellitus where there is high glucose in the blood, diabetes insipidus (non-sweet) is due to a lack of vasopressin in the circulation, which results in the body being unable to reabsorb water in the collecting ducts (> large volumes of dilute urine)

- **Central (cranial)** diabetes insipidus is due to the absence/lack of circulating vasopression, caused by a problem in the production/release of vasopressin from the neurohypophysis.
- **Nephrogenic** diabetes insipidus results from end-organ resistance to vasopressin, either through a lack of V2 receptors, or mutated receptors, or problems with the post-receptor intracellular mechanisms.

**Aetiology of diabetes insipidus**

Central/Cranial is caused by anything that leads to damage of the neurohypophysis. This can be due to injury, surgery, central thrombosis, tumours (intrasellar and suprasellar), and also granulomatous infiltrations of the median eminence
- It can also be idiopathic, or familial (rare)

Nephrogenic can be familial, but this is rare.
- It can also be caused by drugs (e.g. lithium, dimethyl chlortetracycline DMCT), and so drugs such as lithium which is still used in the treatment of various psychiatric disorders have to be considered for the effects of diabetes insipidus.

**Signs + symptoms of diabetes insipidus**

These include...
- Large volumes of urine (polyuria)
• Urine very dilute (hypo-osmolar)
• Thirst and increased drinking (polydipsia)
• Dehydration (and consequences) if fluid intake not maintained
• Possible disruption to sleep with associated problems
• Possible electrolyte imbalance

**Pattern of events:** the lack of vasopressin > polyuria > increase in plasma osmolarity (Na<sup>+</sup>) > reduction in ECF volume > stimulation of osmoreceptors > thirst centre > polydipsia > replacement of ECF volume (this should switch off vasopressin, but in this case there isn’t any so vicious cycle repeats)

The normal (hydrated) range of plasma osmolality (mOsm.kg H₂O⁻¹) is about 280 (270-290). In diabetes insipidus this becomes > 290, and in **polydipsia** this < 270.

- In **psychogenic polydipsia**, a central disturbance combined creates the sensation of thirst and leads to increased drinking (polydipsia), leading to the expansion of extracellular fluid volume and a decrease in plasma osmolality.
  - It also leads to increased urine excretion, and this leads to a reduction of extracellular fluid volume, which increases plasma osmolality. This combined with the central disturbance increases the sensation of thirst and the vicious circle is entered.

**To distinguish between four different patients, a fluid deprivation test is done...**

- **In a healthy person**, fluid deprivation should increase plasma osmolarity, which should increase vasopressin production resulting in more concentrated urine being produced.
- **In a patient with psychogenic polydipsia**, there is a normal vasopressin system, so they can concentrate their urine; but this is not as well as a healthy person. This is because the kidneys will become used to being driven in such a way that the urea is lost in the kidneys so the concentrating ability is lost to a certain degree over time.
- **A person with diabetes insipidus** will not have a functioning vasopressin system, therefore their ability to concentrate urine is lost resulting in extreme dehydration (risk of coma + death if not rehydrated)

**To distinguish between cranial and nephrogenic diabetes insipidus, we use an analogue of vasopressin = DDAVP administration test**

- **In central** diabetes insipidus, there is a lack of vasopressin. However replacing the vasopressin will reverse the effects and the urine concentration will increase.
- **In nephrogenic** diabetes insipidus, there is no lack of vasopressin, but rather a lack of functioning receptor system therefore replacing the vasopressin with DDAVP will have no effect.

**A more rapid test that can be used to distinguish cranial diabetes insipidus from normal, polydipsics or nephrogenics** is the **stimulation with intravenous hypertonic saline test.**

- An infusion with hypertonic saline causes a rapid increase in plasma osmolarity. This should initiate the normal vasopressin release, but in central diabetes insipidus the patient cannot secrete vasopressin therefore there is no response.

**EXCESS OF NEUROHYPOPHYSIAL HORMONES**

The **Syndrome of Inappropriate ADH (SIADH)** by definition is when plasma vasopressin concentration is **inappropriate** for the existing plasma osmolality.

- **Excess vasopressin** causes excess water reabsorption, and retaining more water than normal leads to diluted plasma (relatively less Na<sup>+</sup>)
- Sodium ions play important roles in the body, and **hyponatraemia** is very dangerous.
• The decreased urine volume (small concentrated amount) associated with SIADH means there is actually an increased relative loss of sodium, which worsens the hyponatraemia.
• The body tries to compensate for this by making more urine (natriuresis) to restore urine output, but this decreases sodium still because of the excess vasopressin.

**Signs + Symptoms**

Signs of SIADH include...
• Raised urine osmolarity
• Decreased initial urine volume
• Hyponatraemia due to increased water reabsorption

It can be symptomless, however...
• If $\text{p}[\text{Na}^+] < 120\text{mM}$, there can be generalised weakness, poor mental function + nausea
• If $\text{p}[\text{Na}^+] << 110\text{mM}$, patient may present with confusion, leading to coma and ultimately death

The **causes** of SIADH are varied, but include...
• Tumours (ectopic secretion)
• Neurohypophysial malfunction (e.g. meningitis, cerebrovascular disease)
• Thoracic disease (e.g. pneumonia)
• Endocrine disease (e.g. Addison's disease)
• Physiological i.e. non-osmotic stimuli (e.g. hypovolaemia, pain, surgery)
• Drugs (e.g. chlorpropamide)
• Idiopathic

Once the cause of SIADH is identified (e.g. tumour), then the appropriate **treatment** (e.g. surgery) can be applied.
• The main aim of treatment is to reduce the immediate concern e.g. hyponatraemia. This is does with immediate fluid restriction
• In the longer-term, drugs are used which prevent vasopressin action in the kidneys e.g. lithium, di-methyl-chlor-tetracycline, and also $V_2$ receptor antagonists

### PHARMACOLOGY OF VASOPRESSIN + ITS ANALOGUES

All vasopressin receptors will be activated in response to exogenous vasopressin.

The main **pharmacological action of vasopressin** is **Natureesis** (the process of excretion of sodium in the urine via action of the kidneys) It is V2 mediated, but the mechanism is unclear. It is also only evident with high doses of vasopressin, and may contribute to hyponatraemia.

• Another main action is its **pressor action.** This is V1 mediated, and affects vascular smooth muscle. Not all vascular beds are equally sensitive, but the effect on coronary vessels is important (may cause cardiac ischaemia or angina attacks). Note there are compensatory mechanisms present, which are required to balance the effects of vasopressin otherwise we would be hypertensive
• **Other actions** include...
  • Contraction of non-vascular smooth muscle (e.g. gut motility) via V1a receptors
  • Increased ACTH secretion via V1b receptors
  • Increased Factor VIII and von Willebrand factor production (possible haemophilia treatment) via V2 receptors
• Drugs such as **nicotine** increase vasopressin secretion, and drugs such as **alcohol** or **glucocorticoids** decrease vasopressin secretion.

**Selective Vasopressin Peptidergic Agonists**

These include **Terlipressin** for V1 receptors and **Desmopressin** (DDAVP) for V2 receptors.
Clinically, desmopressin is used in cranial diabetes insipidus, nocturnal enuresis and in haemophilia. It is administered nasally or orally (not broken down by GI proteases); oral producing a prompt sustained decrease in urine volume and increase in urine osmolarity.

NB: the diagram opposite shows a comparison of the activities of vasopressin and desmopressin at V1 + V2 receptors. You can see that DDVAP requires vastly greater quantities to get same effect on V1 receptors because it’s a V2 analogue, but has a much more powerful effect on the V2

- The distribution of desmopressin involves it being retained in extracellular fluid, and the metabolism is hepatic and renal with a typical half-life of about 5 hours.
- The unwanted effects of desmopressin include fluid retention and hyponatraemia; abdominal pain; headaches; and nausea.
  - V2 receptor agonists cause fluid retention, although it is unknown why abdominal pain, headaches and nausea are caused. It could be to do with the high doses affecting the V1 receptor system.

Clinically, terlipressin is useful in haemorrhages in oesophageal varices. Felypressin is also used to prolong the action of local anaesthetics (decreasing the blood flow out of an area concentrates the anaesthetic effect). In both cases the drugs are useful for the vasoconstrictor effect.

**Treatment of nephrogenic diabetes insipidus**

Treatment of nephrogenic diabetes insipidus uses thiazides such as bendroflumethiazide.

- The possible mechanism involves inhibiting the Na+/Cl- transport in the distal convoluted tubule, which leads to a diuretic effect.
- There is volume depletion and a compensatory increase in Na+ reabsorption from the proximal tubule (plus a small decrease in GFR, etc) which causes increased proximal water reabsorption. Consequently, less fluid reaches the collecting duct and there is reduced urine volume. Thiazides reduce urine output by up to 50%, which seems paradoxical as it is a diuretic.

**Treatment of SIADH**

Vaptans are a new class of non-peptide vasopressin analogues, e.g. Tolvaptan (V2 receptor antagonist) used in the treatment of hyponatraemia associated with SIADH, but may be useful in treating congestive heart failure and other conditions.
4. Hypothyroidism + Pharmacology of Thyroid Hormones

Professor Karim Meeran + Dr Glenda Gillies

HYPOTHYROID DISORDERS
Revision of Year 1
(See Year 1 Endo lecture 6 + 7 notes for revision)

- Involves hypothalamic–pituitary thyroid (HPT) axis: Hypothalamus releases thyrotrophin releasing hormone (TRH); Anterior pituitary releases thyrotrophin/thyroid stimulating hormone (TSH); thyroid syntheses + releases iodothyronines (T3 + T4)
- Negative feedback loops: thyrtrophin autoinhibition of hypothalamus, iodothyronine direct + indirect inhibition of anterior pituitary + hypothalamus respectively
- Thyroxine (T4) responsible for BMR

Iodothyronine synthesis + secretion

Uptake of iodide via active transport
1) Iodine from the diet is taken up into blood plasma by the GI tract as iodide ions
2) Hypothalamic TRH causes increased TSH secretion from APG
3) TSH regulates uptake of I- ions from plasma into thyroid follicle cell (across basolateral membrane) via NIS pumps + then into the colloid/follicle lumen (across apical membrane) via PENDRIN pumps
4) TSH binds with its receptor + acts on follicle cell to increase thyroglobulin (TG) synthesis + secretion into the colloid
   - TG is a large glycoprotein (~115 tyrosine molecules)

Iodination
5) TG stimulates thyroid peroxidase + hydrogen peroxide (H2O2) to catalyse the iodination of iodide ions into reactive iodine

Coupling reaction + storage in the colloid
6) Reactive I2 incorporates into the tyrosyl residues of TG, forming MIT (mono-iodo-tyrosyl) + DIT (di-iodo-tyrosyl)
7) Thyroid peroxidase + hydrogen peroxide then catalyses the coupling of MIT + DIT to form T3 (tri-iodo-thyronine) + T4 (tetra-iodo-thyronine)

Endocytosis + secretion
8) TSH stimulates the migration of the TG-bound iodothyronines to the apical membrane of the follicular cell, and this complex is taken up by endocytosis
9) In the follicular cell, the endosome fuses with a lysosome, which releases the TG with its associated tyrosyl residues + T3 and T4 (which are then secreted into the plasma

HYPOTHYROIDISM

Basis of hypothyroidism is that Thyroxine levels decline, with a corresponding increase in TSH.

Clinical Features (all corresponding to decrease in basal metabolic rate) then include...

- Hair dry + brittle
- Lethargy, memory impairment, depression
- Oedema of face + eyes
- Thick tongue, slow speech
- Deepening voice
- Cold intolerance, diminished perspiration
- Cardiomegaly, poor heart sounds, hypertension
- Weight gain with reduced appetite + ascites
- Constipation
- Eventually myxodema coma
**Hypothyroid conditions**

- **Primary hypothyroidism** (myxoedema). The leading cause of this is autoimmune damage to the thyroid (**Hashimoto's disease**). This involves circulating anti-thyroglobulin, anti-thyroid peroxidase and TSH receptor blocking antibodies; as well as the invasion of lymphocytes + macrophages into the thyroid gland. Primary hypothyroidism affects around 1% of the adult population.
- **Consequences of therapy** of thyroid tumours with radioiodine (T4).
- **Iatrogenic hypothyroidism** (resulting from treatment) e.g. glucocorticoids, thiourylenes, lithium.
- **Myxoedema coma** (rare) - a complication of hypothyroidism (T3)

**THYROID HORMONES**

**Actions of T3 + T4**

- Every cell in the body depends on thyroid hormones for regulation of metabolism, i.e. energy production. The actions of T3 and T4 are largely to do with the **metabolism of carbohydrates, fat and protein**. The direct effect is to increase metabolism and sources of energy, and there are also indirect effects via insulin, glucagon, glucocorticoids, catecholamins, and adrenoceptor expression.
  - Thyroid hormones cause basal metabolic rate to increase (oxygen consumption and heat production increase, particularly in the heart, liver and kidneys more than in the gonads, brain and spleen)
  - Cardiac output and heart rate also increase due to sympathetic effects.
- **Growth and development** are also dependent on thyroid hormones, not only in skeletal development, but also in CNS development.
  - Neonatal screening for hypothyroidism means that treatment is possible if necessary to prevent mental retardation and dwarfism (cretinism). The heel prick test may reveal that the neonate needs to be treated with thyroid hormones.

**Mechanisms of action of T3 + T4**

- Thyroid hormone receptors belong to the nuclear receptor superfamily. T4 can be considered a **prohormone**.
- This prohormone doesn’t act on cell surface receptors, it has a specific receptor inside the cell, which transfers into the nucleus and affects DNA production to regulate the activity of that cell.
- T4 is the main circulating thyroid hormone, but it is often converted to T3 which binds more readily to the **intracellular receptor**.

**PHARMACOLOGY OF THYROID HORMONES**

In **replacement therapy**, there are a few drugs that can be used. **Levothyroxine sodium** is usually the drug of choice (T4 analogue), but **Liothyronin sodium** (T3 analogue) can be used for a more rapid action in myxoedema coma by intravenous administration, but this is rare.

**Dosage** of replacement hormones must be monitored by checking **TSH levels** every 6 to 12 months to ensure that the correct dosage is being given. Treatment usually starts with a low dose and works up slowly. Too much will lead to unwanted side-effects of **hyperthyroidism**.

- Signs and symptoms of hyperthyroidism include high BMR, increased temperature, sweating, sensitivity to heat, nervousness, and increased appetite but loss of weight.
- There are many unwanted consequences of enhanced activity in the sympathetic nervous system due to hyperthyroidism including tremor, risk of precipitating angina pectoris, cardiac dysrhythmias or cardiac failure.

Thyroid hormones are **active orally**:

- T4 has a plasma half-life of 6 days, has its peak effect at 9 days, and the half life for the decline of the response is 11 to 15 days
- T3 has a plasma half life of 2 to 5 days, has its peak effect within 1 or 2 days, and has a half life for decline of response of 8 days
These properties illustrate why T3 acts faster and why the hormones accumulate if given daily, therefore treatment begins with a low dose.

There is 10 times more T4 in the plasma than there is T3. Some T4 is converted to T3 in tissues, and further metabolism occurs in the liver (de-iodination, deamination, conjugation). Free and conjugated hormone is secreted in the bile and urine - T3 is cleared in hours, T4 in about 6 days.

**Thyroxine binding globulin**

Almost 100% of the hormone is bound to plasma proteins, mainly thyroxine binding globulin. TBG is a glycoprotein synthesised in the liver (not to be confused with thyroglobulin). Plasma binding proteins increase in pregnancy and on prolonged treatment with oestrogens and phenothiazines. Certain co-administered drugs (e.g. phenytoin, salicytes) compete for protein binding sites.
5. Hyperthyroidism + Drugs which inhibit Thyroxine Synthesis

**HYPERTHYROIDISM**

Graves’ disease is autoimmune disease first described by Robert Graves in 1976, whereby antibodies bind to and stimulate the TSH receptor in the thyroid. The gland is caused to make more thyroxine than is needed and this results in a **smooth goitre** (symmetrically enlarged thyroid) and **hyperthyroidism**.

- It is actually possible to hear blood flowing through the smooth goitre, as it is a very dynamic gland. In hyperthyroidism, the patient feels sweaty and hot; they lose weight with increased appetite, body temperature climbs, muscle wasting, shortness of breath, rapid pulse, tremor, palpitations and tachycardia, breast enlargement as well as sympathetic effects such as lid lag.
- The antibodies bind to muscles at the back of the eyes causing them to swell up - **exophthalmos**. Other antibodies cause **pretibial myxoedema** (hypertrophy). Pretibial myxoedema is the swelling (non-pitting) that occurs on the shins of patients with Graves’ disease in the form soft tissue growth. This is not to be confused with myxoedema, which is hypothyroidism!

Plummer's disease is a **toxic nodular goitre**. This is not an autoimmune condition, but is a **benign adenoma** that is overactive at making thyroxine.

- The patient does not present with pretibial myxoedema, and does not present with exophthalmos either as there are no antibodies involved.
- The tumour results in an asymmetric enlargement of the thyroid, which can be seen on a scintogram.

**Thyroxine** affects the nervous system in many ways. For example, it **sensitises β adrenoceptors** to ambient levels of adrenaline and noradrenaline, thus there is apparent sympathetic activation (i.e. makes catecholamines more potent)

- This leads to tachycardia, palpitations, tremor in the hands and lid lag.
- A **thyroid storm** is a medical emergency as there is a 50% chance of mortality if it is untreated. Blood results taken will confirm hyperthyroidism.
  - Presentation: with **hyperpyrexia** (temperature > 41°C), accelerated tachycardia/arrhythmia, cardiac failure, delirium/frank psychosis, hepatocellular dysfunction + jaundice.

**Viral (de Quervain’s) thyroiditis** presents with painful dysphagia, hyperthyroidism, pyrexia and raised **erythrocyte sedimentation rate** (ESR). The patient will have tender pretracheal lymph nodes and a tender and palpable thyroid, which will be enlarged more on one side.

- A **virus** attacks the thyroid gland causing pain and tenderness, consequently the thyroid stops making thyroxine and makes viruses instead. Thus there is **zero iodine uptake**, and also zero radiiodide uptake.
  - A thyroid scan in Graves’ will be very dark, but a thyroid scan in viral thyroiditis will be blank as there is no iodine uptake. This means the gland is not working.
- Since there is zero radioidine uptake, the **stored thyroxine** is released. Four weeks later the stored thyroxine is exhausted and this results in **hypothyroidism**. After a further month, **resolution** occurs (like in all viral diseases) and the patient then becomes **euthyroid** (normally functioning thyroid gland) again.

**Thyroid cancers**

In the cases of both **papillary** and **follicular** thyroid cancers, radioiodine is taken up. An **adenocarcinoma** is usually bad news, and **medullary** is rare.
Papillary and follicular thyroid carcinomas both may be stimulated to grow by TSH, and they both take up radioiodine.

- Treatment of thyroid carcinoma includes total thyroidectomy, giving large dose of radioiodine (ablation), and giving enough thyroxine to suppress TSH.

**TREATMENT OF HYPERTHYROIDISM + DRUGS WHICH INHIBIT THYROXINE SYNTHESIS**

There are a few treatment options for hyperthyroidism in terms of drugs. **Beta blockade** is very important, and so propranolol can be used. **Anti-thyroid drugs** include Carbimazole and Propylthiouracil. Other than using drugs there is also radioiodine and surgery (thyroidectomy).

**Thiourylenes** (e.g. Carbimazole and Propylthiouracil) are used in the daily treatment of hyperthyroid conditions, mainly for the treatment of a diffuse toxic goitre, Graves’ disease or an exophthalmic goitre in which IgG acts against components of the follicle cell membrane (possibly the TSH receptor) and stimulates T3 + T4 secretion

- NB: Benign neoplasms/toxic nodular goitre/Plummer’s disease is usually treated surgically if necessary.
- They are used as treatment prior to surgery; for the reduction of symptoms while waiting for radioactive iodine to act. The mechanisms of action of thiourylenes are based on the inhibition of thyroperoxidase and peroxidise transaminase and hence T3 and T4 synthesis and secretion. The biochemical effect is within hours but the clinical effect lasts for weeks.
  - The treatment regime may also include propranolol (a non-selective beta blocker) which rapidly reduces tremor and tachycardia.
  - Thiourylenes may also suppress antibody production in Graves’ disease, and reduce the conversion of T4 to T3 in peripheral tissues.
- Unwanted actions of thiourylenes include rashes, headaches, nausea, jaundice + joint pain. Agranulocytosis/granulocytopenia (reduction or absence of granular leukocytes) are rare adverse effects and are reversible on withdrawal of the drug.
- Pharmacokinetics: these are orally active drugs. Carbimazole is pro-drug which first has to be converted to methimazole. The plasma half-life is between 6 and 15 hours, and it has the ability to cross the placenta as well as being secreted in milk.
- Thiourylenes are metabolised in the liver and secreted in the urine

**Iodide** (usually in the form of potassium iodide) doses (30x average daily requirement) can also be given in preparation of patients for surgery, or in severe thyrotoxic crisis (thyroid storm) Its actions include...

- Inhibiting iodination of thyroglobulin
- Inhibiting thyroid peroxidase generation

Thyroid hormone secretion is thus inhibited, and hyperthyroid symptoms will reduce (within 1 or 2 days). The vascularity and size of the gland then reduces within 10 to 14 days.

- Unwanted actions include allergic reaction, e.g. rashes, fever, angioedema
- It is given orally, and has its maximal effects after 10 days of continuous administration

**Radioiodine treatment:** radioiodine is a simple treatment (as it is given as a single dose) whereby radioactive iodine is taken orally as a capsule (containing ~370megabequerels of the 131 iodine isotope). It is used to treat hyperthyroidism and thyroid tumours. The **mode of action** involves the isotope being processed in the same way as stable iodide.

- It is absorbed quickly by the stomach and intestines, then carried in the bloodstream to the thyroid, where it is taken up by the gland and incorporated into thyroglobulin and concentrated in the colloid.
- While in the thyroid gland, the radioactive iodine emits beta-particles (of very short range), which have cytotoxic effects disrupts the function of thyroid follicular cells (specifically) - the more radioactive iodine given, the more cells cease to function. As the cells stop functioning, excessive amounts of thyroid hormones are no longer produced, and symptoms of hyperthyroidism begin to disappear
• NB: radiiodine has a radioactive half-life of 8 days, and its radioactivity is negligible after 2 months with a maximal effect after 2 months.
• Exposure to pregnant patients can have teratogenic effects (disruption of growth + development of fetus), so patients are advised to avoid children and pregnant women.
• If radioiodotopes are required for scans only (as opposed to as a treatment option), then 99-Tc pertechnetate can be used.
  o Otherwise, a very low tracer dose of radiiodine can be used to test thyroid function. This is administered intravenously, and has negligible toxicity.
6. Hyperadrenal disorders + the pharmacology of drugs used to treat adrenal disorders

Professor Karim Meeran + Dr Glenda Gillies

CUSHING’S SYNDROME

Cushing’s syndrome is caused by too much cortisol. The clinical features include centripetal obesity, moon face, buffalo hump, proximal myopathy, hypertension, hypokalaemia, red striae, thin skin, bruising, osteoporosis and diabetes.

- Cushing’s can be caused by taking too many steroids, a pituitary tumour (which causes Cushing’s disease), an ectopic tumour (e.g. in the lung) secreting ACTH, or an adrenal adenoma secreting cortisol.

Investigations to determine the cause of Cushing’s Syndrome include a 24 hour urine collection for urinary free cortisol and a blood diurnal cortisol levels.

- Cortisol is usually highest at 9am and lowest at midnight if asleep in normal patients, but in Cushing's syndrome the cortisol levels are constantly high.
- A low dose dexamethasone suppression test can also be used to investigate Cushing’s
  - Dexamethasone is an artificial steroid, which is taken every 6 hours for 48 hours in a 0.5mg dose
  - Normal patients will respond by suppressing cortisol levels so zero, but Cushing’s patients will fail to suppress their cortisol levels
- A high dose dexamethasone suppression test can be used to distinguish pituitary Cushing’s disease from other types
  - Only pituitary Cushing’s will suppress cortisol to 50%, whereas ectopic ACTH and adrenal tumours will not suppress at all

Diagnosis of Cushing’s is made using the result of the suppression tests.

- For example, a patient may have a basal (9am) cortisol of 800nM. After the low dose test cortisol is 680nM and after the high dose test cortisol is 235nM. This patient has Cushing’s disease.
- Treatment involves pharmacological manipulation of steroids, for example using enzyme inhibitors and receptor blocking drugs.

The treatment of Cushing’s depends on its cause. This may include transphenoidal hypophysectomy (specific for pituitary Cushing’s disease), bilateral adrenalectomy or unilateral adrenalectomy.

- Drugs can also be used, e.g. metyrapone + ketoconazole.

PHARMACOLOGY: INHIBITORS OF STEROID BIOSYNTHETIC ENZYMES (Used for treatment of Cushing’s Syndrome)
Metyrapone inhibits the enzyme 11β-hydroxylase, and in doing so cuts off the production of corticosterone and cortisol. Steroid synthesis in the zona fasciculata and reticularis is arrested at the 11-deoxycortisol stage. 11-deoxycortisol has no negative feedback effect on the hypothalamus and pituitary gland therefore ACTH secretion thus increases and plasma deoxycortisol levels are increased.

**Uses of metyrapone:**
- It is used to treat some cases of Cushing's syndrome, for example bronchial tumours that are inaccessible to surgery. Here the oral doses may be tailored to the corticosteroid production, and corticosteroid replacement therapy may be necessary with high doses.
- Control of Cushing's symptoms prior to surgery

**Unwanted actions:**
- Nausea, vomiting, dizziness, sedation
- Hypoadrenalism + hypertension on long-term administration
- Sedatory effects poses a caution against the impaired performance of skilled tasks e.g. driving
- Hypertension is caused by deoxycorticosterone accumulating in the zona glomerulosa, where it eventually has aldosterone-like (mineralocorticoid) activity > salt retention + hypertension

Trilostane blocks the activity of 3β-hydroxysteroid dehydrogenase and therefore prevents the production of glucocorticoids, mineralocorticoids and sex steroids. So aldosterone, corticosterone, cortisol and androstenedione production are all cut off.

**Uses of trilostane:**
- Used in cushing’s syndrome, particularly in primary hyperaldosteronism. Note It is not easy to tailor a dose to corticosteroid production. Circulating corticosteroids and plasma electrolytes are monitored and replaced with glucocorticoids and mineralocorticoids when necessary.
- Is it also used in the reduction of sex steroid hormone production, e.g. in post-menopausal breast cancer which has relapsed after initial therapy with anti-oestrogens.

**Unwanted actions:**
- Nausea, vomiting, diarrhoea
- Flushing

Ketoconazole is mainly used as an antifungal agent. At higher concentrations, it inhibits steroidogenesis due to non-specific inhibition of cytochrome P450 enzymes (most abundant in smooth endoplasmic reticulum). It blocks the production of glucocorticoids, mineralocorticoids and sex steroids.

**Uses of ketoconazole:**
- Similar to metyrapone; used in the treatment + control of symptoms of Cushing’s
- NB: is orally active

**Unwanted actions:**
- Nausea, vomiting, abdominal pain
- Alopecia (loss of hair)
- Gynaecomastia (breasts on men)
- Oligospermia (low concentration of sperm in semen)
- Ventricular tachycardias
- Liver damage (this is possibly fatal, therefore liver function needs to be monitored clinically + biochemically)
- Reduced androgen production

Aminoglutethamide works by inhibiting the conversion of cholesterol to pregnenolone (very toxic). This blocks the production of glucocorticoids, mineralocorticoids and sex steroid hormones.

**Uses of aminoglutethamide:**
- Malignant adrenocortical carcinoma
- Malignant of prostatic cancer (NB: corticosteroids must be replaced)
- NB: it is orally active
**CONN’S SYNDROME**

Conn's syndrome is a benign adrenal cortical tumour in the zona glomerulosa, which causes aldosterone to be in excess, leading to hypertension and hypokalaemia.

- **Diagnosis** is made when the patient presents with primary hyperaldosteronism (increased serum aldosterone levels). Secondary hyperaldosteronism is excluded as the renin-angiotensin system should be suppressed.

- **Treatment** of Conn's syndrome has various options. An aldosterone receptor antagonist such as spironolactone can be used, or surgical intervention may be appropriate to remove the adenoma. If the patient presents with bilateral adrenal hyperplasia, they can stay on spironolactone.

**PHARMACOLOGY: ALDOSTERONE RECEPTOR ANTAGONISTS** (Used for treatment of Conn’s Syndrome)

Spironolactone is used in primary hyperaldosteronism (Conn’s) as well as in the treatment of oedema, congestive heart failure, nephritic syndrome and cirrhosis of the liver.

- It is a prodrug which is rapidly converted to canrenone; a competitive antagonist of the mineralocorticoid receptor. This blocks Na+ reabsorption and K+ excretion in the kidney tubules (potassium sparing diuretic).

- It is orally active and is given daily in a single or divided dose. It is highly protein bound and undergoes hepatic metabolism.

- **Unwanted actions** include menstrual irregularities, gynaecomastia (androgen receptor binding), and also GI tract irritation

- **Contraindications** of use include renal and hepatic disease

**PHAEOMYOCYTOPTOMAS**

Phaeoeyocytomas are tumours of the adrenal medulla which secrete catecholamines (adrenaline + noradrenaline).

- **Clinical features** include hypertension in young people and episodic severe hypertension (after abdominal palpation). It is more common in certain inherited conditions.

- Severe hypertension can cause myocardial infarction or stroke, and high adrenaline can cause ventricular fibrillation and death, thus this is a medical emergency.

**Management**: a phaeochromocytoma will eventually need surgery, but the patient needs careful preparation as anaesthetic can precipitate a hypertensive crisis.

- Alpha blockade is the first therapeutic step. Patients may need IV fluids as this commences

- Beta blockade is then added to prevent tachycardia

**Key facts**: 10% of phaeochromocytomas are extra-adrenal (sympathetic chain), 10% are malignant, 10% are bilateral, and are extremely rare.

**Treatment** of disorders of the adrenal medulla include SNS antagonists (see lecture), e.g. propranolol, phentolamine + phenoxybenzamine
7. Hypoadrenal disorders
Professor Karim Meeran

**INTRODUCTION + REVIEW**

NB: Review year 1 hypoadrenal disorders (Endo Lectures 8-9, Tutorial 5)

**Synthesis of Adrenocortical steroids**

- Cholesterol is the precursor to all steroid hormones
- All the enzymes involved in the synthesis pathway are hydroxylase enzymes (learn the ones above in green)
- The Hypothalamo-pituitary-adrenal axis is key to the production of cortisol in the adrenal cortex.
- Having an understanding of the synthesis pathways of adrenocortical steroids allow you to work out all the rare causes of adrenal failure
- NB: deficiencies of enzymes will cause an increased flux through the other branches of the pathway

**ADRENOCORTICAL FAILURE**

**Causes of adrenocortical failure**

There are two cases where the cause of adrenocortical failure is due to the adrenal glands being destroyed:

- **Tuberculosis Addison's disease** (most common worldwide)
- **Autoimmune Addison's disease** (most common in UK)

Another cause is due to enzymes in the steroid synthetic pathway not working:

- **Congenital Adrenal Hyperplasia**

**Signs of adrenocortical failure** include hyperpigmentation (of mucous membranes, skin hair), autoimmune vitiligo, weight loss, muscle weakness, hypotension
Consequences of adrenocortical failure include:

- hypotension
- Loss of salt in urine
- Increased plasma potassium (hyperkalaemia)
- Fall in glucose due to glucocorticoid deficiency (hypoglycaemia)
- High ACTH due to cortisol deficiency > increased pigmentation.
  - This increased pigmentation is because ACTH is made from the precursor POMC.
  - This is synthesised and broken down to ACTH and MSH (melanocyte stimulating hormone), endorphins, enkephalins and other peptides
  - MSH is responsible for the hyperpigmentation
- Death due to severe hypotension

Tests for Addison's
Addison's can be tested for if 9am cortisol is low and ACTH is high. A short synACTHen test is done (synthetic ACTH), whereby 250μg of synACTHen is given intramuscularly, and the cortisol response is measured.

- For example if 9am cortisol was 100 (normal 270-900), and after an intramuscular injection of synACTHen, cortisol at 9.30am could be found as 150 (normal >600), in which case the patient can be diagnosed with Addison's.

CONGENITAL ADRENAL HYPERPLASIA
The commonest cause of congenital adrenal hyperplasia is 21-hydroxylase deficiency. This can be complete or partial. It is an inherited enzyme deficiency whereby cortisol and aldosterone are consequently deficient.

In complete 21-hydroxylase deficiency, the patient can survive for less than 24 hours or so as sodium will be lost in urine:

- Presentation as a neonate will be Addisonian crisis.
- Sex steroids and testosterone are in excess as the 17-OH progesterone follows through to becoming sex steroids. Before birth (while in utero), the foetus gets steroids across the placenta.
- Girls might have ambiguous genitalia (virilised by adrenal testosterone)

In Partial 21-hydroxylase deficiency, cortisol and aldosterone are slightly low.

- There is a high ACTH and a high 17-OH progesterone, which leads to there being a high testosterone and again sex steroids are in excess.
- Patients in this case, however, can present at any age as they survive.
- The main problem later in life is Hirsutism and virilisation in girls and precocious puberty in boys due to adrenal testosterone
- Other problems include acne, variable pigmentation, muscular arms and legs

There are some anomalies with 11-deoxycorticosterone, which in fact behaves like aldosterone.

In 11-hydroxylase deficiency, cortisol and aldosterone are deficient with 11-deoxycorticosterone, sex steroids and testosterone in excess.

- In excess, 11-deoxycorticosterone causes hypertension and hypokalaemia
- Sex steroids also cause virilisation

In 17-hydroxylase deficiency, cortisol and sex steroids are deficient, while 11-deoxycorticosterone and aldosterone are in excess

- Problems with this include hypertension, hypokalaemia, sex steroid deficiency and hypoglycaemia (due to glucocorticoid deficiency)
8. Adrenal Steroids as Anti-inflammatory and Immunosuppressive Drugs

Dr Pat Cover

Control of adrenal steroid production is through hypothalamo-pituitary-adrenal axis. This is influenced by many factors including circadian stimuli and stress (Review Endo Year 1 Lectures 8-9 + Tutorial 5)

- These stimuli lead to CRH being released from the hypothalamus, which stimulates the release of ACTH from the anterior pituitary which in turn stimulates cortisol secretion from the adrenal gland. Cortisol then exerts a negative feedback (both indirect + direct) on the HPA axis
- Aldosterone is secreted from the adrenal gland when it is stimulated by the Angiotensin II (Review the Renin-Angiotensin System)

The glucocorticoids (cortisol and synthetic cortisol analogues) are an important group of drugs and are used:

- for replacement therapy in patients with adrenocortical insufficiency
- to provide replacement therapy and quench ACTH (and hence adrenal androgen production) in congenital adrenal hyperplasia
- in differential diagnosis of Cushing’s syndrome
- to control inflammation
- to produce immunosuppression in hypersensitivity, autoimmune disease and transplant patients (prevention of rejection)
- in the treatment of neoplastic disease
- to mature the foetal lung prior to pre-term birth

INFLAMMATION

Inflammation can be both helpful and harmful. It is a powerful defence response, which enables the body to eliminate pathogens and trigger defence mechanisms. However inflammatory responses may be harmful if they are inappropriate and cause damage to healthy tissue, for example hypersensitivity reactions eg anaphylaxis, chronic disease eg rheumatoid arthritis.

Characteristics of inflammatory responses

At the macroscopic level, inflamed tissue is red, hot, swollen and painful. This is due to the microscopic inflammatory responses:

- Damaged cells release histamine which lead to vasodilation of blood vessels
  > increased blood > heat + erythema (redness)
- Exudation of plasma + leukocytes > swelling (local oedema)
- Some inflammatory mediators activate sensory afferents > pain

NB: erythema multiforme is a sign of acute inflammation

If the pathogen persists, the condition proceeds to chronic inflammation which additionally involves:

- Tissue damage (cell death or ulceration)
- Impaired tissue function (eg restricted joint movement, bronchospasm)
- Local repair processes (proliferation of local cells, becoming fibrous connective tissue)
- Scarring

Mechanisms of inflammation can be innate or acquired.

1. Innate (non-immunological) responses comprise immediate but non-specific vascular and cellular events which are triggered by pro-inflammatory mediators derived from plasma (e.g. complement factors) and from local and invading cells (e.g. histamine, eicosanoids, nitric oxide and cytokines). These are modulated by anti-inflammatory substances.
Vascular events:
- Histamine release > vasodilation + increased blood flow
- Increased capillary permeability > plasma exudate
- Activation of enzyme cascades > release of inflammatory mediators eg complement, bradykinin. These stimulate sensory afferents > pain, increase mediator release + vascular permeability, cause bacterial lysis whilst attracting/activating phagocytic cells

Cellular events:
- local cellular events include the release of pro-inflammatory mediators from mast cells, involvement of tissue macrophages, release of vasodilators + other mediators from endothelial cells > angiogenesis and fibrous tissue development from fibroblasts
- in addition, cellular events which involve migration of cells from the blood into tissue occur. These include polymorphonuclear leukocytes (which kill pathogens via toxic oxygen), monocytes (which are transformed into macrophages), and platelets (which contribute to tissue repair)

2. Acquired (specific) immunological responses are the 2nd, slow in onset but specific line of defence. Such responses may be initiated by antigenic products of invading microorganisms which reach the lymph nodes; hypersensitivity (inappropriate) reactions to exogenous substances; or hypersensitivity reactions to endogenous proteins that are normally innocuous (i.e. autoimmunity).

The induction and effector phases of lymphocyte activation:
Key points: main cells involve are T + B cells (both derived in bone marrow, but T cells mature in the thymus).

1) Antigen is presented by APC (located in all tissues; engulf pathogen, break down into basic components and present to surface) to naïve CD4+ T-helper cells
2) CD4+ T helper cell recognises antigen, binds (requiring co-stimulatory factors to increase binding affinity) > activation of the CD4+ T-helper cell
3) Activation > response by release of IL-2 (autocrine) and expression of IL-2 receptors
4) IL-2 causes proliferation of the CD4+ T-helper cell into a clone of activated T cells (Th0)
5) Th0 cells then differentiate into either Th1 or Th2 cells
   a. Th1 cells produce IL-2 and IFN-γ > proliferation + differentiation into CD8+ T-cells
   b. Th2 cells produce IL-4 which acts on B cells > B cell proliferation + antibody production
6) CD8+ T-cells effect cell-mediated reactions, whereas B cells are involved in antibody-mediated reactions
Drugs used to treat inflammation include non-steroidal anti-inflammatory drugs (NSAIDs) like aspirin, and steroidal anti-inflammatory drugs like glucocorticoids.

GLUCOCORTICOIDS
Glucocorticoid use as anti-inflammatory and immunosuppressive drugs
Glucocorticoids inhibit the early and late stages of inflammation by modifying vascular and cellular events.

- In terms of **modifying vascular events**, they inhibit the vasodilator response and reduce fluid exudation
- The effects on **cellular events** include reducing influx/activity of PMNs, inhibiting recruitment/activity of monocytes, inhibiting angiogenesis, blocking clonal proliferation of T cells and inhibiting fibroblast function

They also **inhibit the production of pro-inflammatory mediators** including histamine, eicosanoids, cytokines, complement components and nitric oxide, as well as **enhancing production of anti-inflammatory proteins** eg annexin 1.

**Extracellular matrix formation** is also supressed by glucocorticoids. This is due to...
- Reduction in matrix protein production eg collagen, GAGs
- Enhancement of degrading enzyme production eg collagenases

The **molecular basis of glucocorticoid action** is via:

**Blockade of eicosanoid production**
Eicosanoids are arachidonic acid derivatives which act as signalling molecules involved in inflammation, immunity and in the CNS.

- There are four families of eicosanoids; prostaglandins, prostacyclins, thromboxans and leukotrienes.
- They are pro-inflammatory, thus anti-inflammatory drugs often act by downregulating their synthesis.

**Inhibition of cell-mediated immune responses**
Examples of drugs

Hydrocortisone (the approved name for cortisol) is used clinically in the treatment of inflammatory disease.

- However, when given systemically in doses sufficient to produce a beneficial clinical effect, it binds to mineralocorticoid receptors (MR) and produces unwanted aldosterone-like effects.
- Modifications to the cortisol molecule have led to the development of analogues with a higher degree of selectivity for the glucocorticoid receptor, for example prednisolone and dexamethasone.

Pharmacokinetics

- **Administration** is either oral or parenteral (intravenous or intramuscular)
  - if required. In addition, they may be administered locally, for example, to the respiratory tract (inhalation), to the skin (as ointments or creams) or in inflamed joints by local injection.
- **Distribution** varies depending on the drug:
  - Hydrocortisone is ~95% bound to corticosteroid binding globulin (plasma protein)
  - Prednisolone binds to CBG
  - Dexamethasone only weakly binds to albumin
- **Metabolism** occurs mainly in the liver, with reduction of the A ring being the principle step.
  - Other modifications and conjugation also occurs before excretion via bile and urine
- The **duration of action** of the glucocorticoids persists well beyond clearance of the drug:
  - Hydrocortisone has a half-life of ~1hr, but its DOA is ~8hrs
  - Prednisolone has a DOA of ~12hrs
  - Dexamethasone has a duration of ~40hrs

Clinical uses

Clinically, glucocorticoids are used in treating disorders of the HPA axis (Addison's disease, congenital adrenal hyperplasia, differential diagnosis of Cushing's syndrome/disease). They are also used in pregnancy to mature the foetal lung for pre-term birth. Other uses include:

- **Anti-inflammatory/immunosuppressive therapy:**
  - Asthma
  - Inflammatory conditions of the skin, nasal mucosa, ear, eye, joints
  - Autoimmune/inflammatory disease, e.g. rheumatoid arthritis
  - Other autoimmune disease, e.g. myasthenia gravis
  - To prevent rejection following organ or bone marrow transplants

- **Treatment of neoplastic disease:**
  - In combination with cytotoxic drugs in specific malignancies, e.g. acute lymphocytic leukaemia
  - To reduce cerebral oedema in patients with brain tumours
  - As a component of anti-emetic treatment with chemotherapy
  - To elevate mood in terminally ill subjects

Adverse/Unwanted Effects

The unwanted effects of glucocorticoids are usually due to the effects of prolonged glucocorticoid excess, which leads to iatrogenic Cushing's syndrome.

The typical symptoms will include potassium loss, sodium and water retention, hypertension, muscle wasting, centripetal obesity, moon face, buffalo hump, hyperglycaemia (leading to steroid diabetes), increased appetite, osteoporosis, increased risk of infection, poor wound healing, easy bruising, impaired growth, disorders of menstruation, mood changes.

Ways to **minimise the unwanted effects** include:

- Administer locally where possible
- Use minimum effective dose
- Use a GR-selective steroid
- Use ACTH in children to reduce growth suppression
9. Therapeutic Use of Adrenal Steroids

Dr Pat Cover

REVISION
The adrenal cortex produces 3 types of steroid hormone:

- **Glucocorticoids** (principle steroid = cortisol) from the zona fasciculata
- **Sex steroids**, mainly androgens and oestrogens (principle steroid = DHEA) from the zona reticularis
- **Mineralocorticoids** (principle steroid = aldosterone) from the zona glomerulosa

Principle physiological actions of adrenal steroids:
You cannot survive without a basal level of cortisol (level rises before waking, and in response to stress). It has important roles in metabolism, host-defence, bone turnover, mood and behaviour. These actions can be divided into two broad categories:

- **Permissive actions** (occurs during non-stress levels) maintain body systems in a state to be able to respond to stress, eg up-regulation of cytokine receptors in preparation for combating infection
- **Protective actions** (occur during high stress concentrations) keeps the body's response to stress in check, ie prevents an overshoot. For example suppression of production of inflammatory mediators to prevent shock (hypotension, oedema and tissue damage)

Aldosterone is key in the control of blood pressure; in response to hypotension it promotes Na+ retention and K+ excretion
There are various hypotheses about why sex steroid levels also rise in response to stress

Clinical uses of glucocorticoids:

- For replacement therapy in patients with adrenocortical insufficiency
- To provide therapy and to quench ACTH and hence adrenal androgen production in congenital adrenal hyperplasia
- In the differential diagnosis of Cushing's syndrome (dexamethasone suppression test)
- To control inflammation
- To produce immunosuppression in hypersensitivity, autoimmune disease and transplant patients (prevention of rejection)
- In the treatment of neoplastic disease
- To mature the foetal lung prior to preterm birth

NB: Adrenal androgens are not used clinically in the UK, but aldosterone derivatives have an important place in the treatment of certain types of adrenocortical insufficiency.
CORTICOSTEROID RECEPTORS
Corticosteroid receptors are members of the nuclear receptor super-family: they are intracellular receptors that when bound, translocate to the nucleus and alter DNA transcription.

Comparison of the two types of corticosteroid receptors

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<tr>
<th>Property</th>
<th>Glucocorticoid Receptors (GR)</th>
<th>Mineralocorticoid Receptors (MR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distribution</td>
<td>Wide</td>
<td>Discrete (concentrated in the kidney and sweat glands)</td>
</tr>
<tr>
<td>Steroid specificity</td>
<td>Selective for glucocorticoids</td>
<td>Do not distinguish between cortisol + aldosterone</td>
</tr>
<tr>
<td>Affinity for cortisol</td>
<td>Low affinity</td>
<td>High affinity (but generally not activated, as most cortisol present in the circulation near MR receptors has been converted to inactive cortisone by 11β-hydroxysteroid dehydrogenase (11βHSD))</td>
</tr>
</tbody>
</table>

NB: when present in high concentrations cortisol gains access to the receptors and exerts mineralocorticoid activity.

Drugs acting on GR + MR
- Cortisol (hydrocortisone) - glucocorticoid with mineralocorticoid activity at high doses
- Prednisolone - glucocorticoid with weak mineralocorticoid activity
- Dexamethasone - synthetic glucocorticoid with no mineralocorticoid activity
- Fludrocortisone - aldosterone analogue used as an aldosterone substitute

NB: these drugs are all very similar in structure, with only slight differences accounting for their differences in receptor activity

Pharmacokinetics of Corticosteroids
- Administration is either oral or parenteral (intravenous or intramuscular except fludrocortisone). NB: aldosterone is not effective orally
- Distribution is via plasma proteins (CBG + albumin). Hydrocortisone is 90-95% bound, and the binding strength decreases from prednisolone > dexamethasone > fludrocortisone which only binds weakly to albumin
  - Weakly binding drugs are more bioavailable, therefore are more potent, eg dexamethasone and fludrocortisone. These both cross the placenta and are secreted in milk
- Metabolism is hepatic, with a reduction of the A ring being the principle step. Further modifications + conjugation occurs before they are excreted via bile and urine
- Duration of action determines the dosing frequency
  - Hydrocortisone + fludrocortisone = t1/2 ~1hr, duration ~8hrs
  - Prednisolone = duration ~12hrs
  - Dexamethasone = duration ~40hrs

CORTICOSTEROID REPLACEMENT THERAPY (refer to tutorial 4)
The uses of corticosteroid replacement therapy are as follows...
- Primary adrenocortical failure (Also known as chronic adrenal insufficiency/Addison’s disease) is due to a failure of the adrenal cortex > inability to produce cortisol, aldosterone and sex steroids
  - Treat with titrated doses of oral hydrocortisone + fludrocortisone, with electrolyte level + BP monitoring
- Secondary adrenocortical failure is due to ACTH deficiency > lack of cortisol but not aldosterone, eg in hypopituitarism
  - Treat with titrated hydrocortisone
- Acute adrenocortical failure requires urgent parenteral treatment of Addisonian Crisis. This includes:
  - IV/IM infusion of hydrocortisone or dexamethasone every 6hrs
- Saline infusion
- Glucose infusion

- **Congenital adrenal hyperplasia** results from a **congenital lack of steroid synthetic enzymes**. The most common deficiency is 21-hydroxylase (in 95% of cases) > no cortisol or aldosterone synthesis, with corresponding increase in intermediates + androgens. However if hypertension suggests an 11-B-hydroxylase deficiency > build of of 11-deoxycorticosterone + 11-deoxycortisol. In both deficiencies, the patient will have increased ACTH levels.
  - **Objectives of therapy** = replace cortisol, suppress ACTH production + replace aldosterone
  - Therapy is also optimised by measuring adrenal androgens

- **Iatrogenic adrenocortical failure** = **drug induced** failure in patients on long-term high dose corticosteroid treatment eg for chronic RA. These patients have a **suppressed HPA axis**, therefore require protection in surgery (high stress) and should carry a steroid card.

**Additional measures** in subjects with adrenocortical failure

Key parameters to remember are **normal cortisol=20µg/day**, with an increase to **200-300µg during stress**

Treatment of adrenocortical failure must be increased when patients are vulnerable to stress, for example:

- **Minor illness** > 2-3x normal dose
- **Surgery** > IM hydrocortisone (pre-med + at 6-8hr intervals)
- In preparation for **adrenalectomy or hypophysectomy**
10. Oral Contraceptives, HRT + SERMs

Professor Glenda Gillies

**REVISION**
For recap of female hypothalamo-pituitary-gonadal axis, refer back to Year 1 Endo Lectures 10 + 11

Key points from the **menstrual cycle**:
- Hypothalamus releases neuropeptide GnRH
- Anterior Pituitary Gland releases LH + FSH
- FSH stimulates follicle development
- LH acts with FSH to increase oestradiol + stimulate ovulation
- Follicular phase: increase in oestradiol (first slowly, then exponential), which eventually causes the LH surge > ovulation
- Once ovulation occurs, you get the luteal phase of the cycle > progesterone secretion

**OESTROGENS + PROGESTERONES AS DRUGS**
There are some **clinically useful oestrogens** and progestogens/progestins used in practice, namely there is **17-β oestradiol** and its esters (e.g. **valerate**)

**Pharmacokinetics**
- **Oestradiol** and its esters are well absorbed but they undergo extensive first pass metabolism
- Oestradiol esters may be given by injection, usually intramuscularly in oil. The oil vehicle delays absorption, maintains plasma levels over extended periods and prolongs the duration of action.
- Conjugated oestrogens are excreted in bile and urine.

**Types of Oestradiol**
There are 3 types of oestradiol:
- **Oestriol** – a naturally occurring, orally active oestrogen that is produced by the placenta during pregnancy. This is not generally used for oestrogenic properties.
- **Oestrone sulphate** – conjugated oestrogen which is the main post-menopausal estrogen. This may be natural, or synthetic = Premarin. This is hydrolysed to the more active oestrogen within peripheral tissues
- **Ethinyl oestradiol** – semi-synthetic oestrogen based on the same structure of oestradiol but with an ethinyl group on C17. This is resistant to metabolism therefore is the drug of choice

Most oestrogens can also be administered via **transdermal skin patches**, as oestrogens readily cross membranes and a skin patch avoids first pass metabolism. In terms of **bioavailability**, 70% of circulating oestrogens are bound to plasma proteins such as sex steroid hormone binding globulin and albumin

**Clinically used progestogens** fall into two groups:
- **Progestosterone and its analogues** such as **medroxyprogesterone acetate**. Progesterone is poorly absorbed, and is also rapidly metabolised by the liver. It can be given by intramuscular injection in an oily vehicle as a depot preparation.
- **Testosterone analogues** such as **norethisterone**. A variety of orally active synthetic progestogens are available (like norethisterone). These bind to SHBG and albumin in circulation. Synthetic progestogens are variously metabolised to other biologically active steroids, eg testosterone and oestrogen

**CONTRACEPTIVES**
There are 3 **types of contraceptives**:
- Combined oral contraceptives (COCs)
- Progesterone only contraceptives
- "emergency" contraceptives
Basic concepts

Physiological actions of oestrogen in the HPG axis
- -ve and +ve feedback controlling LH surge and ovulation
- increase uterine + fallopian tube smooth muscle contractility
- reduce viscosity of cervical secretions to favour sperm penetration
- stimulates endometrial proliferation and glandular secretions

Physiological actions of progesterone:
- changes mucosal secretions in the fallopian tubes (important for nourishment of fertilized ovum)
- thickens cervical mucus (hostile to sperm)
- decreases myometrial contractility (favours implantation and development of embryo)
- stimulates development of lobules and alveoli in mammary tissue (primed by oestrogens, prepares for lactation)

Combined oral contraceptives (COCs)
These are usually a combination of an oestrogen (ethinyl oestradiol) with a second - or third - generation progestogen (e.g. norethisterone)
This combination provides additive and synergistic pharmacology to maximise efficacy at minimal drug concentrations to suppress ovulation via multiple mechanisms. These include:
- Feedback actions of progesterone in the hypothalamus and pituitary, supressing menstrual cycline
- Progesterone thickens cervical mucus which provides a hostile environment to sperm
- Oestrogen up-regulates progesterone receptors, enhancing the sensitivity to progesterone
- Oestrogen counteracts the androgenic effects of synthetic progesterone, thus preventing masculinization
- Oestrogen also contributes to negative feedback at the hypothalamus and pituitary, by synergising with progesterone

A combined oral contraceptive is usually taken for 21 days and then stopped for 7 days. At doses that produce inappropriate (unphysiological) hormone concentrations, fertility is disrupted. Monophasic means there is one concentration taken throughout. Triphasic means there are 3 step-wise changes in the oestrogen/progesterone ratio

Unwanted effects of oestrogen
- Increased clotting factors > increased incidence of thromboembolic disease
- Increased proliferation of the endometrium > increased risk of cancer
- Breast discomfort (+ query increased risk of breast cancer, but this is controversial)
- Increased salt and water retention may cause oedema, and contribute to hypertension and weight gain
- Nausea (triggering vomiting centre of brain; like morning sickness)
- Headaches
- Increased weight gain (fat deposition + oedema)

Progestogen-Only Contraceptives
These may be used when oestrogens are contra-indicated in patients. For example, if they have CVS problems, a history of thrombosis, if they are prior to major surgery or during lactation. They are administered orally, or long acting preparations may be given by deep intramuscular injection (e.g.medroxyprogesterone acetate / Depot-Provera) or via an intra-uterine system.

“Emergency” Contraception
Also known as the post-coital/morning after pill, these are combined oestrogen and progestogen (prescription only) pills or progestogen alone (over the counter) pills, at doses higher than those used in normal combined oral contraceptives.
- Two doses are taken 12 hours apart, beginning as soon as possible and within 72 hours of intercourse.
Menopause, HRT + SERMs

Menopause

- **Definition**: permanent cessation of menstruation resulting from the loss of ovarian follicular activity and 12 months of amenorrhea at the time of midlife (~51 years, range 45-55). In post-menopausal women, there is less negative feedback within the HPG axis.
  - **Climacteric**: the period of transition from predictable ovarian function to the post-menopausal years
  - **Premature menopause** (or premature ovarian failure) is menopause occurring before the age of 40, and this occurs in 1% of women.
    - Causes of premature menopause includes surgical and autoimmune (family history & investigate for other associated autoimmune conditions)
    - Other causes of secondary amenorrhea should be excluded, such as pregnancy or a pituitary problem like a prolactinoma.

- **Symptoms**
  - Begins with *irregular cycles and hot flushes*. Women experience an increased pulse rate and profuse sweating. These flushes often last about 4 minutes, and occur at night (insomnia). 80% of women are affected in this way. Most flushes resolve within a year.
  - **Psychosocial symptoms**, for example depression, mood swings and loss of energy
  - **Translucent thin skin** (reduced oestrogen > reduced collagen)
  - **Decreased libido**
  - **Urogenital atrophy** (urgency, nocturia, increased UTI, dryness of the vagina, discomfort with intercourse = dyspareunia)
  - usually diminish/disappear with time

- **Complications**
  - **Osteoporosis** – oestrogen deficiency > loss of bone matrix, with associated decrease in bone mass and increase in fracture risk
  - **Cardiovascular disease** – women are relatively protected against CV disease before menopause, but have the same risk as men by age 70

Treatment of Menopause

HRT = hormone replacement therapy

- **Oestrogen-only** HRT is used for women who have had a hysterectomy, for example Premarin
- **Combined** HRT is used to prevent endometrial hyperplasia in all other women, eg PremPro, CEEs + medroxyprogesterone
- HRT has various **formulations**: oral, transdermal patch/gel, percutaneous slow release implant, intranasal spray or intravaginal oestrogens
- **Advantages** include a delay in osteoporosis. Indications for use include severe vasomotor symptoms (flushes)
  - There have been queries about the use of HRT in reduction of IHD, but this is not proven and is not a licensed use. This is true for IHD, alzheimer’s, and colon cancer
- **Disadvantages**: increased risk of endometrial carcinoma and breast cancer. Also increased risk of gallstones, venous thromboembolism, and CVA
Whether or not to take hormone replacement therapy is the patient’s decision after education and counselling. Benefits of treatment should outweigh the risks, but 50% of women discontinue HRT after 1 year. It is common to treat normal menopausal women for 5 to 7 years, and to treat premature menopause until a normal menopause age.

**Tibolone**
- synthetic prohormone of oestrogen, progestogen and androgen (weak)
- As a synthetic prohormone it is a "designer HRT"
- It provides relief of vasomotor symptoms of menopause, and is as effective as HRT. It increases bone density, and we are still waiting on data regarding fractures and the link with endometrial and breast cancer.

**SERMs = selective oestrogen receptor modifying drugs**
- These are effectively designer oestrogens which bind to oestrogenic receptors (a + B) with high affinity, and therefore displace oestradiol
- This means that they activate oestrogen metabolic pathways (agonist), but in some tissues by binding to the receptor they effectively block the ability of oestrogen (antagonist)

**Related drugs**
**Tamoxifen** is a commonly used SERM that has agonist activity in bone and uterus, but antagonist activity in breasts
- It is an anti-cancer drug; its anti-oestrogenic effects on breast tissue mean it is used to treat oestrogen-dependent breast tumours and metastatic breast cancers
- It has oestrogen-like effects on the liver (lowers cholesterol), bone (increases density) and endometrial tissue (increased risk of cancer)
- Side effects include:
  - Endometrial changes, including hyperplasia, polyps + cancer
  - Bone pain with bony metastases
  - Hotflushes
  - Menstrual irregularities
  - GI disturbances

**Raloxifene** has antagonist effects on bone, but antagonist effects on breast and uterus
- It is used in the treatment and prevention of postmenopausal osteoporosis
- Advantages include a reduced risk of vertebral fractures and a decrease in risk of breast cancer
- Disadvantages include an increased risk of fatal stroke, venous thromboembolism, and no reduction in vasomotor symptoms

**Clomiphene** is a fertility drug used in women who are infertile due to a lack of ovulation
- It is anti-oestrogenic in the hypothalamo-pituitary axis, as it blocks normal negative feedback to increase GnRH, LH and FSH secretion
- It is administered in the first 5 days of the menstrual cycle to induce ovulation
- Side effects include ovarian hyperstimulation > abdominal discomfort, hot flushes, nausea, vomiting and headaches
- Multiple pregnancies may occur as a result of the clomiphene treatment; therefore follicles are tracked by ultrasound scanning
11. Endocrine Infertility
Dr Waljit S Dhilo

REVISION

Hypothalamic-pituitary-gonadal axis

In the male:
- GnRH released from hypothalamus in a pulsatile manner > stimulates release of LH + FSH from the pituitary gland (positive feedback)
- LH stimulates testosterone production from the Leydig cells of the testis
  - Testosterone is responsible for development of secondary sexual characteristics + aiding spermatogenesis
  - Testosterone negative feedback at hypothalamus + pituitary
- FSH stimulates the Sertoli cells in the seminiferous tubules to produce sperm and inhibin A + B
  - Inhibin negative feedback for FSH secretion from pituitary

In females there is a 28 day menstrual cycle consisting of the follicular phase, ovulation and the luteal phase

Follicular phase:
- GnRH released from hypothalamus in a pulsatile manner > stimulates release of LH + FSH from the pituitary gland (positive feedback)
- LH stimulates ovarian oestrogen + progesterone
- FSH stimulates follicular development + inhibin
  - Inhibin inhibits FSH release
- By day 10, the leading follicle develops into the Graffian follicle
- Oestrogen initially negatively inhibits LH + FSH secretion, then its exponential increase results in positive feedback > LH (+FSH) surge which induces ovulation

Luteal phase:
- If implantation does not occur, the endometrium is shed = menstruation
- If implantation occurs, pregnancy follows

INVESTIGATION OF FERTILITY

Infertility is the inability to conceive after 1 year of regular unprotected sex
- This occurs in 1 in 6 couples.
- In 30% of cases it is caused by abnormalities in the male, in 45% of cases the female, and in 25% of cases the cause of abnormality is unknown.

Primary gonadal failure is where there is a high GnRH and therefore also high LH + FSH. However the testes/ovaries are unresponsive, leading to low testosterone or oestradiol

In hypopituitary disease, there is low GnRH > low FH/LH > low testosterone/oestradiol

DISORDERS IN THE MALE

Hypogonadism
- Clinical features include a loss of libido, impotence, small testes, decreased muscle bulk and osteoporosis
- It can be caused by hypothalamic-pituitary disease (hypopituitarism), for example a tertiary hypopituitarism is Kallmann’s syndrome caused by a low GnRH
  - In a 16 year old boy Kallman’s syndrome would present with testes originally undescended and a low to normal stature as well as anosmia.
- This is a genetic cause of hypogonadism; however it can also be caused by illness and being underweight
- Another cause is primary gonadal disease, which is usually congenital eg Klinefelter’s syndrome (XXY) where there is 5α-reductase deficiency. It can be acquired, for example by testicular torsion or chemotherapy
• Hyperprolactinaemia is another cause of hypogonadism, as is androgen receptor deficiency.

Investigations
• History: symptoms
• Blood work (LH, FSH, testosterone, prolactin)
  o LH, FSH, testosterone low = hypopituitary disease
  o LH, FSH high, testosterone low = primary gonadal failure
• Sperm count: 10^6 per ejaculate is normal
  o Azoospermia = absence of sperm in ejaculate
  o Oligospermia = reduced numbers of sperm in ejaculate
• Chromosomal analysis (looking for Klinefelter’s XXY)

Treatment
• Replacement testosterone therapy is important for all patients (and for muscle bulk + osteoporosis)
• Replacement hormones for fertility if hypothalamo-pituitary disease:
  o GnRH administered in pulses
  o Dopamine agonist used to counteract associated hyperprolactinaemia

Androgens
Site of Androgen production
• Interstitial leydig cells of testes
• Adrenal cortex (male + females)
• Ovaries
• Placenta
• Tumours

Main actions of testosterone
• Development of the male genital tract (therefore important for in utero development)
• Maintenance of fertility
• Control of secondary sexual characteristics
• Anabolic effects (muscle, bone strength + bulk)

Mechanism of action of testosterone
• In the circulation, testosterone is 98% protein bound following tissue-specific processing
• 5α-reductase converts testosterone into dihydrotestosterone (DHT) which acts via the androgen receptor (AR), therefore this enzyme is important in fertility
• Aromatase converts testosterone into 17β-oestradiol (E2) which acts via the oestrogen receptor (ER) e.g. in the brain and in adipose tissue. The mechanism of action of both these hormones is via nuclear receptors.

Clinical uses of testosterone
• In adulthood can be used to increase lean body mass, muscle size/strength, bone formation/mass, libido + potency
• It will not restore fertility, which requires treatment with LH/FSH and pulsatile GnRH to restore normal spermatogenesis

DISORDERS IN THE FEMALE
Fertility disorders in the female can be caused by 3 main things:
• Amenorrhoea
• Polycystic ovarian syndrome (POCS)
• Hyperprolactinaemia
Amenorrhea is the absence of periods. Primary amenorrhea means there is failure to begin spontaneous menstruation by the age of 16 years. Secondary amenorrhea means absence of menstruation for 3 months in a woman who has previously had cycles. Oligomenorrhoea is irregular long cycles.

- The main cause of amenorrhea is pregnancy/lactation. However a cause can be ovarian failure
- Ovarian failure can be premature ovarian failure, or due to ovariectomy or chemotherapy
  - Can also be due to ovarian dysgenesis (Turner’s 45X where a chromosome is lacking)
- Investigations:
  - Pregnancy test
  - Blood work: LH, FSH, oestradiol + day 21 progesterone
    - The 28 menstrual cycle means that hormone levels vary, therefore single measurements are not very useful
    - In a normal cycle, there is an increase in progesterone at day 21
  - prolactin levels
  - thyroid function tests
  - androgens (high levels indicate tumour)
  - chromosomal analysis
  - ultrasound of ovaries and uterus
- treatment:
  - 1st, treat the cause
  - Patients with primary ovarian failure are infertile and will thus require HRT (counselling post-diagnosis required)
  - Hypothalamic-pituitary disease can be treated with GnRH and gonadotrophins

Polycystic Ovarian Syndrome has an incidence of 1 in 12 women of reproductive age

- It is associated with an increased cardiovascular risk and also insulin resistance
- can be diagnosed by seeing polycystic ovaries on an ultrasound scan, if the patient presents with anovulation, and by measuring clinical/biochemical androgen excess (need to have 2 out of 3)
- clinical features of PCOS include hirsutism, menstrual cycle disturbance and increased BMI
- Treatment:
  - Metformin: an oral diabetes medicine that helps control blood glucose.
  - Reverse circadian prednisolone, which suppresses pituitary ACTH production which drives adrenal androgen production
  - Clomiphene: an anti-oestrogenic fertility drug that binds to the oestrogen receptors in the hypothalamus, thereby blocking the normal negative feedback > increased GnRH + gonadotrophin release
  - Gonadotrophin therapy

Hyperprolactinaemia

Unlike most endocrine systems whereby positive stimulation occurs, the main regulator of prolactin secretion is in fact inhibitory; dopamine. TRH in fact has a much smaller contribution to controlling secretion

- The use of anti-emetics, anti-psychotics and other dopamine-antagonist drugs can cause hyperprolactinaemia
- A prolactinoma may also be the cause, which may co-secrete growth hormone > associated acromegaly
- The final cause may be infundibulum compression due to a pituitary adenoma, which causes a failure of dopamine release
- Other causes include: PCOS, hypothyroidism, oestrogens, pregnancy, lactation, or it can be idiopathic
Clinical features include:
  - Galactorrhoea
  - Reduced GnRH secretion/LH action

First line treatment is to treat the cause, for example to stop taking dopamine antagonist drugs.
  - Instead, dopamine agonist drugs should be given to treat the hyperprolactinaemia (Bromocriptine and Cabergoline).
  - A prolactinoma can be treated with dopamine agonist therapy, and rarely pituitary surgery.
12. Endocrinology of Pregnancy
Professor John Laycock

FERTILISATION
Fertilisation is the process by which spermatozoon meets ovum. The journey from the testis to the oviduct is a long one; 100,000x its own length. It is also one taken very much against all odds of success, as less than 1/100,000,000 actually reaches the ovum.

The male reproductive tract
- Within the tract, most tubular fluid is reabsorbed in the rete testis and early epididymis under oestrogen control (produced by sertoli cells)
- Nutrients and other molecules, eg glycoproteins, are secreted into the epididymal fluid under the control of androgens. This:
  - Provides energy for the impending possible journey of the sperm
  - Coats the sperm surface
NB: these secretory products are vital for the sperm maturation process

Ejaculation
Semen is ejaculated into female tract (usually the vagina, sometimes into the cervical canal). It consists of:
- Spermatozoa (15-120x10^6/ml)
- Seminal fluid (2-5ml)
- Leukocytes
- (potential viruses, eg Hep B, HIV)

Seminal Fluid has a small contribution of components such as inositol, carnitine and glycercyolphosphorylcholine from the epididymis/testis
However it is mainly from the accessory sex glands, including the seminal vesicle (2/3rds) and prostate (1/3rd)
  - The seminal vesicles contribute fructose and fibrinogen
  - The prostate contributes cirtic acid, acid phosphatatse, fibrinogenase, and fibrinolytic enzyme
Other accessory organs include the ampulla and bulbourethral glands

Spermatozoon Activation
Taken from the seminiferous tubule, spermatozoa are quiescent and incapable of fertilizing an ovum.
- Taken from the vas deferens, spermatozoa are capable of movement, but only have limited capability for fertilizing an ovum. This is known as activation
- However, full activity and fertilizing capability is only achieved within the female reproductive tract. This is known as capacitation

Capacitation of sperm has a number of steps
1) Loss of glycoprotein coat
2) Change in surface membrane characteristics, leading to the acrosome reaction when in close proximity to an ovum
3) Further whiplash movements of the tail
NB: this takes place in the ionic and proteolytic environment of the oviduct, ie it is oestrogen-dependent.
All components of capacitation are Ca^{2+} dependent. Note that only 1% of the spermatozoa in ejaculate enter the cervix.
In the **acrosome reaction**, there is a Ca\(^{2+}\) influx into sperm stimulated by **progesterone** following the binding of sperm to ZP3 (short lived). This results in the Ca-dependent acrosome reaction.

- This enables an exposed spermatozoon binding site to bind to a second glycoprotein (ZP2)
- Subsequently the spermatozoon penetrates the zona pellucida (e.g. by releasing hyaluronidase and other proteolytic enzymes).

**Fertilisation** normally occurs within the fallopian tube.

It results in the expulsion of a **second polar body**, and leads immediately to the **zonal reaction**

- In the zonal reaction, cortical granules release molecules which degrade the zona pellucida (including ZP2 and ZP3) to prevent further binding of other sperm
- Once diploidy is established, the zygote starts dividing to form the initial **2-cell conceptus**

**Development of the Conceptus**

The conceptus continues to divide as it moves down the Fallopian tube to the uterus. This process takes 3 to 4 days. Until implantation the developing conceptus receives its nutrients from uterine secretions. This free-living phase can last for about 9 to 10 days

- The conceptus first compacts to an 8 to 19 cell **morula**, then into a blastocyst (inner cell mass > embryo, outer tropheoblast > chorion)
- Transfer of blastocyst from fallopian tube to uterus is facilitated by increasing progesterone to oestrogen ratio (luteal phase)
- Blastocyst then establishes physical and nutritional contact with maternal tissues

**Implantation**

Implantation in humans is invasive. It involves the initial **attachment** phase when the outer trophoblast cells contact uterine surface epithelium. Within in a few hours, it results in **decidualization** of the underlying uterine stromal tissue. This requires **progesterone** domination in the presence of oestrogen

**Attachment**

**Leukaemia inhibitory factor (LIF)** from the endometrial secretory glands (and blastocyst) stimulates adhesion of the blastocyst to endometrial cells.

**Interleukin-11 (IL11)** is also released into uterine fluid and may be involved.

**The Decidualisation Reaction**

Decidualisation involves the invasion of the underlying uterine stromal tissue by the trophoblast cells of the blastocyst. Within hours of initial contact, there is:

- Increased vascular permeability in the invasion region associated with oedema of tissues
- Localised changes in intracellular composition and progressive sprouting and growth of capillaries
- The decidualisation reaction

Factors involved in the decidualisation reaction include mainly interleukin-11 (IL11), histamine, prostaglandins, and TGFβ (which promotes angiogenesis)
PREGNANCY

Hormones during pregnancy

During the first 5-6 weeks of pregnancy, the maternal ovaries release gonadal steroids that are essential for the developing fetoplacental unit

- The circulating progesterone and oestradiol concentrations are high and rising during this period, and the release of maternal LH and FSH are inhibited by negative feedback.
- The stimulatory role of gonadotrophins on the corpus luteum is taken over by human chorionic gonadotrophin (hCG), which is produced by the developing implanting blastocyst (syncytiotrophoblast)

From day 40 onwards, the role of the ovaries and corpus luteum is taken over by the fetoplacental unit.

Maternal hormones

- Maternal hormones such as thyrotrophin, corticotrophin, prolactin, growth hormone, iodothyronines, adrenal steroids and PTH increase.
- Others like gonadotrophins decrease, and hGH decreases as the placental hGH-Variant increased towards term.

Endocrine control of Parturition
Endocrine control of Lactation

Hypothalamus → Pituitary

Neurohypophysis Adenohypophysis

Oxytocin Prolactin

Milk ejection

Milk synthesis

SUCKLING (stimulus)
13. Endocrine Bone Disorders
Professor John Laycock + Dr Glenda Gillies

VITAMIN D DEFICIENCY

Vitamin D metabolites

1,25(OH)\textsubscript{2}D\textsubscript{3} (Calcitrol) is crucial in regulating absorption of calcium. Its principle effect is to stimulate intestinal absorption of Ca\textsuperscript{2+} (+Mg\textsuperscript{2+} and PO\textsubscript{4}\textsuperscript{3-}), providing the ions necessary for normal bone mineralisation

- It also stimulates osteoclast formation from precursors in bone; stimulating their activity as well as simulating osteoblast activity > matrix protein synthesis

Symptoms

Vitamin D deficiency states = lack of mineralization in bone. This results in “bone softening”, bone deformities, bone pain, and severe proximal myopathy.

- In children, this presents as Rickets
- In adults, this presents as Osteomalacia

Causes

NB: there is an increased concern in Vit D deficiency due to its increasing prevalence. This is partially due to the ageing population, whose diet is often poor and a lack of mobility restricts their exposure to the sun (UV).

A reminder of Vitamin D synthesis is shown opposite. A fault can occur at a variety of points in the diagram on the right, which will cause vitamin D deficiency:

- Lack of UV light
- Poor ergocalciferol intake in the diet
- Liver disease (impact on 25 OH-D3)
- Renal disease (impact on 1α-hydroxylase)
- Malabsorption disorders in the gut
- Receptor defects (which may affect Ca\textsuperscript{2+} absorption, maintenance or calcitrol negative feedback on PTH)

Diagnosis

A deficiency in either exogenous or endogenous Vit D will result in...

- low plasma 25(OH)D\textsubscript{3} and low plasma Ca\textsuperscript{2+} (unless secondary hyperparathyroidism has been induced when it may appear normal)
- PTH levels will be high (no negative feedback)
- Plasma phosphate will be low

NB: The radiological findings associated with deficiency are variable, for example you may see widened osteoid seams.

Renal Failure

Decreased renal function has two main effects that lead to hypocalcaemia. These include:

- Decreased calcitrol, which causes decreased calcium absorption
- Decreased phosphate excretion > increased plasma phosphate. This leads to extraskeletal calcification

The resulting hypocalcaemia has two main effects:

- Decreased bone mineralisation > osteitis fibrosa cystica (softening + deformities of bone)
- Increased PTH secretion > increased bone resorption > osteitis fibrosa cystica
VITAMIN D EXCESS

Vitamin D intoxication can lead to hypercalcaemia and hypercalciuria due to increased intestinal absorption of calcium. It can also occur as a result of:

- Excessive treatment with active Vit D metabolites, eg when treating chronic renal failure
- In granulomatous disease eg sarcoidosis, where tissue converts 25(OH)D$_3$ to the active 1,25(OH)$_2$D$_3$

PAGET’S DISEASE

Paget's disease is defined as increased bone metabolism (localised but disorganised). This usually shows a slow progression, and is characterised by abnormal large osteoclasts.

- Up to 30% autosomal dominant
- Evidence for viral origin eg measles
- Men + women affected equally
- Presents ~50-60years; >10% of people over the age of 60 are affected but are asymptomatic

Symptoms include:

- Increased Vascularity (warmth over affected bone).
- Increased osteoclast/osteoblast activity; initially osteoclast activity (increased deformity and fracture risk); followed by increased osteoblast activity (thickening of deformed bone).
- Pelvis, femur, spine, skull (associated with hearing loss), and tibia are most commonly affected.
- Fractures.
- Bone pain (nerve entrapment, joint involvement)

Diagnosis

- Plasma calcium normal
- Plasma alkaline phosphatase increased

NB: Radiology demonstrates variable features including loss of trabecular bone, increased density and deformity. A radioisotope (Technetium) scanning of the bone can indicate the areas of involvement.

PHARMACOLOGY + THERAPEUTICS OF BONE DISORDERS

Calcium Salts eg calcium chloride + calcium gluconate

NB: bone acts as the storage vessel for >95% of the body’s calcium. 65% of this bone mass is the inorganic calcium hydroxyapatite crystals which fill the spaces between collagen fibrils. Collagen fibrils are the organic component which fills the remaining 35% of bone mass

- Plasma Ca$^{2+}$ is maintained between 2.3-2.6mmol/L, and this can be affected by bone mineralisation/resorption (build up/breakdown).
  - Osteoblasts synthesize osteoid and participate in mineralisation/calcification of osteoid (bone deposition)
  - Osteoclasts release lysosomal enzymes which break down bone (bone resorption)
- PTH + Vit D > increased bone resorption > increased plasma calcium
  - PTH increases osteoclast activity + modulates osteoblast activity
  - Calcitonin > decreased plasma calcium by inhibition of intestinal absorption + bone resorption

Calcium salts can be used to treat:

- Osteoporosis: a condition of reduced bone mass and a distortion of bone microarchitecture which predisposes to fracture after minimal trauma. Pre-disposing conditions to osteoporosis include:
  - Post-menopausal oestrogen deficiency
  - Age related deficiency in bone homeostasis, eg raised PTH levels + decreased osteoblast levels
  - Raised glucocorticoid levels, eg iatrogenic Cushing’s syndrome (GC reduce osteoblasts + stimulate osteoclasts)
• **Hypocalcaemias** due to:
  o Dietary deficiency of calcium
  o Malabsorption of calcium
  o Hypoparathyroidism > low PTH
  o Hypocalcaemic tetany (low calcium > increased Na⁺ entry into neuronal ~ muscle cells > hyperactivity > tetany)

NB: calcium salts may want to be used in **combination** with Vitamin D preparations, bisphosphonates, and/or calcitonin. In post-menopausal osteoporosis, they may be combined with oestrogens + calcitonin.

• **Cardiac dysrhythmias** caused by severe hyperkalaemia

**Calcium chloride** is administered via slow iv infusion (due to its local effects)
  • This may cause peripheral vasodilatation, a cutaneous burning sensation and a moderate fall in bp > reflex tachycardia
  • DO NOT administer orally as it is a gastric irritant
  • DO NOT inject intramuscularly as it could cause tissue necrosis

**Calcium gluconate** can be administered in two ways (advantage)
  • Orally (does not cause gastric irritation)
  • Intravenously (for severe hypocalcaemic tetany)

**Bisphosphonates/Disphosphonates** are analogues of pyrophosphate, eg sodium etidronate, alendronate

Their **mechanism of action** is to:
  • Inhibit recruitment and promote apoptosis of osteoclasts
  • Indirectly stimulate osteoblasts

Their **uses** include:
  • Treating Paget’s disease
  • Management of hypercalcaemias associated with malignancy
  • in cancer treatment to delay bone metastases
  • osteoporosis induced by high glucocorticoids

**Pharmacokinetics:**
  • orally active but poorly absorbed, therefore take on empty stomach
  • accumulates at site of bone mineralisation + remains part of bone until resorption takes place, therefore duration of action = months/years
  • excreted unmetabolised in urine

**Unwanted actions** include:
  • Increase in non-mineral osteoid > increased pre-disposition to fractures
  • Gastric pain + GI disturbance
  • Oesophagitis
  • Bone pain

**Oestrogenic Compounds** (oestrogen receptor [ER] ligands) including:
  • **Oestrogens**, eg ethinyl estradiol (ER agonist)
  • **Anti-oestrogens**, eg tamoxifen (antagonises ERs in breast, but has estrogenic activity in bone)
  • **SERMs**, eg raloxifene

These are used specifically in the prevention of post-menopausal osteoporosis, as they inhibit osteoclast recruitment and oppose PTH

**Unwanted actions:**
  • Increased risk of endometrial cancer, therefore bone-selective SERMSs used preferentially
  • Increased risk of breast cancer (controversial)
  • Minor GI problems
  • Small increased risk of venous thromboembolism + pulmonary embolism
Calcitonin is a 32α peptide hormone produced by the parafollicular cells of the thyroid gland
- It acts via a 7-transmembrane, G-protein coupled receptor to reduce calcium and phosphate resorption
- Calcitonin decreases plasma calcium, and has a negative impact on osteoclasts and kidney 1α-hydroxylase.

Its uses include:
- Paget's disease to relieve bone pain and neurological complications
- Osteoporosis (both post-menopausal and glucocorticoid induced)
- In treating hypercalcaemias, for example:
  - Primary hyperparathyroidism (Excess PTH)
  - Vitamin D intoxication
  - Neoplasias, malignancies, osteolytic bone metastases
- Treatment of life-threatening hypercalcaemic emergency (arrhythmias, coma, cardiac arrest)
  - Treatment involves rehydration, diuresis, bisphosphates + calcitonin

Pharmacokinetics:
- Synthetic salmon and human calcitonin are available for clinical use
- The route of administration is usually subcutaneous or intramuscular in Paget's disease, or intranasally in post-menopausal osteoporosis
- Resistance due to antibody formation may develop after a few months.

Unwanted actions:
- Inflammatory reaction at sight of injection
- Nausea, vomiting
- Facial flushing
- Tingling sensation in hands
- Unpleasant taste in the mouth

Vitamin D is a fat soluble vitamin that plays an important physiological role in maintaining plasma calcium and regulating cell growth
It is used in the treatment of diseases associated with hypocalcaemias

Ergocalciferol is used:
- To prevent osteomalacia, rickets (Vit D deficiency) and disorders of vitamin D absorption
- To treat hypocalcaemias associated with hypoparathyroidism (preferential to PTH treatment = expensive, parenteral + more side effects)

Calcitriol is used to treat osteodystrophy arising as a result of decreased calcitriol production due to chronic renal failure

Mechanism of action:
- Calcitriol binds to its IC receptors > enhanced transcription of Ca\(^{2+}\) transporter in the small intestine > increased calcium + phosphate absorption
- In the kidney it increases reabsorption of calcium and phosphate
- In the bone it promotes mineralisation, growth + remodelling
- Role in cell growth/differentiation, especially bone marrow
Other drugs used to treat hypercalcaemias:

- **Diuretics**, eg saline diuresis + loop diuretics
- Diuresis is used to reduce plasma Ca\(^{2+}\) in emergency, eg in sarcoid lesions of the reticulo-endothelial system
- **Anti-inflammatory glucocorticoids** eg prednisolone
- Used to normalise plasma Ca\(^{2+}\), especially when due to sarcoid (granulomatous disease involving lesions of the lymphatic system and tissues)
14. Oxytocic Drugs

Professor Glenda Gillies

Clinical uses of drugs acting on the pregnant uterus:
- Induction + augmentation of labour (increase contractions)
- Control of post-partum haemorrhage and uterine atony
- Therapeutic abortion
- Delay of premature labour (Reduce contractions/relax the uterus)

Drugs acting on the Pregnant Uterus

Oxytocics (increase motility + contractions)
- Oxytocin
- Ergometrine
- Prostaglandins

Abortifacients
- Prostaglandins
- Progesterone receptor antagonists

Tocolytics (relax uterine smooth muscle)
- B-adrenoceptor agonists (esp B2 subtype salbutamol)

OXYTOCIN

Oxytocin is structurally similar to arginine vasopressin; the replacement of Phe$_3$ + Arg$_8$ for Ile$_3$ + Leu$_8$ is responsible for the change in selectivity + specificity of oxytocin when compared to AVP.

Control of production of oxytocin involves the hypothalamic-posterior pituitary axis
- Both the paraventricular nucleus (PVN) and supraoptic nucleus (SON) of the hypothalamus produce vasopressin + oxytocin (This production is regulated separately)
- The hypothalamic nuclei send their fibres down to the posterior lobe of the pituitary gland, with the nerve terminals secreting the neuropeptides into the general circulation

Principal Actions

Uterus: stimulates rhythmic contraction of the uterine smooth muscle (myometrial cells) during labour; a propulsive contraction (via PGE$_2$ production) which causes the baby to move down the birth canal
- Cervical + vaginal stimulation > cervical dilation (ensuring the baby fits) + positive nervous feedback to hypothalamus to produce more oxytocin
- Uterine distension also has a positive feedback to the hypothalamus
- During gestation, the uterus is not very responsive to oxytocin (preventing pre-term labour), but at term, the uterus becomes highly responsive to oxytocin
  - This is due to the fall of progesterone (which suppresses response) and increased oestrogen (which enhances response)

Mammary Gland: the neuro-endocrine reflex arc of oxytocin release begins with the stimulus of suckling, and receptors around the nipple signal via the neural afferent limb to the hypothalamus. The endocrine efferent limb results in:
- Contraction of the myoepithelial cells of the mammary gland > milk ejection

NB: these actions pose a therapeutic advantage

Cardiovascular (occurs in pharmacological concentrations of oxytocin)
- Transient peripheral vasodilation > reflex tachycardia > arrhythmias + possible cardiac arrests (unwanted effect)
- Constriction of umbilical arteries + veins, therefore preventing post-partum haemorrhage (positive effect)

Renal (present with pharmacological oxytocin): Anti-diuresis > blood volume expansion + relative Na$^+$ levels fall = secondary hypotraemia > tissue malfunction (unwanted effect)

CNS (additional physiological effect): parental bonding hormone, trust, social recognition
Clinical uses
- **Induction of labour** at term via controlled iv infusion
- **Prevention of post-partum haemorrhage**, via slow iv injection/infusion
- **Facilitation of milk** let-down via intranasal spray (Avoids GI/Hepatic metabolism)

Pharmacokinetics
- **Administration** via iv infusion/slow injection or intranasal spray
- **Distribution**: it is a small, mainly water soluble, peptide therefore accumulates in the extracellular fluid. It acts on the 7transmembrane receptors (G-protein receptors)
- **Metabolism** by liver, kidney + plasma (placenta-derived enzyme)
  - Half-life is ~5mins

Unwanted effects due to overdose
- Umbilical vessel constriction could compromise placental exchange of oxygen + nutrients > foetal distress
- Foetus forced against undilated cervix (despite use of oxytocin) > trauma to baby + uterus
- Transient (++serious) peripheral hypotension with reflex tachycardia
- Excessive anti-diuresis > water-intoxication of mother and foetus

ERGOMETRINE
**Ergot** is a fungus-derived compound which comprises many biologically active alkaloids
- Some of these act like dopamine, and can be used to treat Parkinson’s, hyperprolactinaemia + migraine
- The principal oxytocic agents is ergometrine, and this is the main drug used in the late stage of labour

Principal actions
- Increased tone + prolonged series of contractions of the myometrium
- Constriction of umbilical/placental vessels

Clinical use
- It is only useful in the 3rd stage of labour (once head + shoulders have been delivered), and is administered intramuscularly with/without oxytocin
  - After delivery of the shoulders, if it appears to be a high risk of post-partum haemorrhage, it is administered intravenously
  - If post-partum atony of the uterus is present, oral ergometrine is administered

NB: contraindications include pregnancy prior to 3rd stage labour, pre-eclampsia + other vascular disease

Pharmacokinetics
- **Administration** is IM, IV or oral depending on reasons for use
- It is well distributed
- **Metabolism** is hepatic, and the duration of action is 3-4 hours

Unwanted effects
- Abdominal pain
- Hypertension
- Angina pain
- Nausea/vomiting
**PROSTAGLANDINS**
Prostaglandins can be used as oxytocics and abortifacients

**Biosynthesis**
Arachidonic acid derivative →

**Actions on the uterus**
- Stimulate **contractions** throughout pregnancy (this is different to oxytocin)
- Induce **cervical ripening**

**Prostaglandin preparations:**
- **Dinoprostone:** PGE2 (vasodilator)
- **Gemeprost:** PGE1 derivative
- **Carboprost:** 15-methyl - PGF2α (vasoconstrictor)

**Clinical uses** of prostaglandins in pregnancy:
- **Induction of abortion:** dinoprostone - intravaginally administered as a gel or tablet
- **Induction of cervical ripening**: at term dinoprostone is used, but prior to abortion gemeprost vaginal pessaries are used
- **Post-partum haemorrhage in those resistant to oxytocin and ergometrine:** carboprost intramuscular administration

**Unwanted effects** of prostaglandins include potentiation of actions of oxytocin, nausea, vomiting, diarrhoea, hypertension (PGF2α), hypotension (PGE2), and pyrexia.

**PROGESTERONE RECEPTOR ANTAGONISTS**
Progesterone receptor blockers e.g. mifepristone (RU486) are competitive antagonists of progesterone at the progesterone receptor with weak agonist activity.
- Clinically, this can be **used** to **induce an early therapeutic abortion** (up to 63 days).
- The **mechanism** is mifepristone involves blockade of uterine progesterone receptors, which causes detachment of the blastocyst and reduced hCG production.
  - Consequently there is reduced progesterone production by the ovarian corpus luteum, and this leads to accentuated decidual breakdown and increased uterine prostaglandin production.
  - Mifepristone is also used in **softening and dilating the cervix** prior to suction abortion, or in **therapeutic abortion at 13 - 20 weeks** in combination with gemeprost.

**Pharmacokinetics:**
- **Administration:** oral, good bioavailability
- **Distribution:** enters cells but distribution limited by plasma protein binding
- **Metabolism:** hepatic + enterohepatic, t1/2 20-40hrs
- **Excretion:** mainly in the faeces

**Unwanted effects** include vaginal bleeding and headache

**TOCOLYTICS**
Tocolytics, e.g B2-adrenoceptor agonists increase intracellular cyclic AMP > relaxation of the uterine muscle
DEFINITION + CLASSIFICATION

Classification
- **T1DM**: single organ autoimmune disease, causing destruction of the B-islets of Langerhans which in turn leads to complete insulin deficiency (early onset)
- **T2DM**: metabolic disorder characterised by reduced insulin secretion and increased insulin resistance. (late onset)
- **MODY**: maturity onset diabetes of the young. Early onset diabetes caused by a single gene defect which behaves like T2DM
- **LADA**: latent autoimmune diabetes of adulthood behaves like T1DM
- **Other** causes of diabetes include secondary to endocrine diseases, eg Cushing’s

Ambiguity with classification
- LADA may be confused with Type 2 diabetes from onset, and T1DM from presentation
- Rise in childhood obesity > T2DM presenting in childhood and adolescence
- Diabetic ketoacidosis now feature of T2DM
- Monogenic diabetes, eg MODY, can present phenotypically as T1DM or T2DM
- T2DM (previously non insulin-dependent) now often requires treatment with insulin

Current classification based on underlying aetiology (WHO 1985)
- **T1DM**: environmental trigger + trigger + genetics > autoimmune destruction of islet cells
- **T2DM**: obesity + genetics + B-cell failure > insulin resistance

PATHOGENESIS OF TYPE 1 DIABETES MELLITUS

Type 1 Diabetes Mellitus is an organ specific autoimmune disease

**Immunological Mechanism**
The immune basis for T1DM is important because:
- It is associated with an increased prevalence of other autoimmune disease
- It is associated with an increased risk of autoimmunity in relatives
- It results in a complete destruction of B-cells, whereas T2 is just deficient
- It is increasingly difficult to distinguish T1 and T2 diabetes, but auto-antibodies are useful
- Immune pathophysiology leads clinicians to suggest that immune modulation may offer new treatments

NB: in type 1 diabetes, a microscope will show an immune infiltrate into the B-cell islets

**Genetic susceptibility**
The genetics of T1DM are pretty well understood, with specific HLA molecules acting as either protective or risk-inducing for T1DM.

<table>
<thead>
<tr>
<th>HLA-DR allele</th>
<th>Protective</th>
<th>Risk inducing</th>
</tr>
</thead>
<tbody>
<tr>
<td>DR2</td>
<td>DR6 (neutral/protective)</td>
<td>DR1 (slight)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DR3 (significant)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DR4 (significant)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DR5 (slight)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DR8 (neutral/slight)</td>
</tr>
</tbody>
</table>

However genetics is not sufficient to explain T1DM; there also appears to be environmental triggers (suggested by the fact that onset appears to be seasonal, ie less in summer)
Markers
There are markers that can be used to determine an underlying autoimmune response indicative of T1DM.

<table>
<thead>
<tr>
<th>Marker</th>
<th>Abbr</th>
<th>Description</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Islet Cell Cytoplasmic Autoantibodies</td>
<td>ICA</td>
<td>Measures a group of islet cell autoantibodies targeted against a variety of islet cell proteins</td>
<td>One of the most common islet cell autoantibodies detected at onset of disease Detected in 70-80% of newly diagnosed type 1 diabetics</td>
</tr>
<tr>
<td>Glutamic acid decarboxylase autoantibodies</td>
<td>GADA</td>
<td>Tests for autoantibodies directed against beta cell antigen, but NOT specific to beta cells</td>
<td>Also detected in about 70-80% of newly diagnosed type 1 diabetics</td>
</tr>
<tr>
<td>Insulinoma-associated-2 autoantibodies</td>
<td>IA-2A</td>
<td>Tests for autoantibodies directed against beta cell antigens, but NOT specific</td>
<td>Detected in about 60% of type 1 diabetics</td>
</tr>
<tr>
<td>Insulin autoantibodies</td>
<td>IAA</td>
<td>Autoantibody targeted to insulin (only antigen highly specific to beta cells)</td>
<td>Detected in about 50% of type 1 diabetic children, not common in adults IAA does not distinguish between autoantibodies that target the endogenous insulin, and the antibodies produced against exogenous insulin</td>
</tr>
</tbody>
</table>

- If ICA, GADA, and/or IA-2A are present in a person with symptoms of diabetes, the diagnosis of type 1 diabetes is confirmed. Likewise, if IAA is present in a child with diabetes who is not insulin-treated, type 1 diabetes is the cause.
- If no diabetes-related autoantibodies are present, then it is unlikely that the diabetes is type 1. Some people who have type 1 diabetes will never develop detectable amounts of islet autoantibodies, but this is rare. The majority of people, 95% or more, with new-onset type 1 diabetes will have at least one islet autoantibody.
- Because GADA and IA-2A assays are automated, these tests are generally more available than ICA testing, which is labor-intensive and requires considerable expertise in interpretation.
- Islet autoantibodies may also be seen in people with other autoimmune endocrine disorders such as Hashimoto thyroiditis or autoimmune Addison disease.

Immune modulators in the treatment of type 1 diabetes
There have been various attempts at modifying the immune response in type 1 diabetes, but the current problem is that by the time T1DM is identified, it is highly likely that 80-90% of pancreatic function has been lost, and at this stage it is too late to start modifying the immune response.
- However there is a suggestion that drugs may slow the failure of insulin secretion, when they are started early on

CLINICAL PRESENTATION
The onset of type 1 Diabetes is fast, and usually has a characteristic presentation which is obvious. This is very different to type 2 Diabetes, which is often insidious in onset and asymptomatic at presentation

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyuria</td>
<td>Dehydration</td>
</tr>
<tr>
<td>Polydipsia</td>
<td>Cachexia</td>
</tr>
<tr>
<td>Nocturia</td>
<td>Hyperventilation (insulin deficiency &gt; metabolic acidosis &gt; hyperventilation)</td>
</tr>
<tr>
<td>Blurring of vision (hyperglycaemia &gt; change in</td>
<td></td>
</tr>
</tbody>
</table>

Immune modulators in the treatment of type 1 diabetes
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CLINICAL PRESENTATION
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BIOCHEMICAL BASIS
Metabolism can be broadly divided into 2 key concepts:
- Eat + store energy
- Release stores + use energy

Lots of hormones are involved in the release of energy stores and conversion to glucose, but very few use the nutrition you have taken in and convert the glucose into useful stores.

The biochemical aspects of diabetes all result from the effects of insulin deficiency. In the absence of insulin there is:
- Increased hepatic output
- Reduced muscle uptake and utilisation
- Proteolysis
- Lipolysis
- Ketogenesis
- Dyslipidaemia
- Impaired growth

Glucose metabolism

Look at diabetes/metabolism notes from last year!!
TREATMENT

The **aims** of treatment in type 1 diabetes are to:

- Reduce early mortality; exogenous insulin is VITAL
- Avoid acute metabolic decompensation
- Prevent long term complications such as retinopathy, nephropathy, neuropathy and vascular disease
  - These are NOT the long-term complications of diabetes, but rather the long-term complications of hyperglycaemia

**Diet** alone is not a feasible solo treatment for diabetes, but it is very important in the long-term management plan. A healthy diet prolongs the use of the limited quantity of insulin, and should consist of:

- Reduced calories as fat
- Reduced calories as refined/processed carbohydrate
- Increased calories as complex carbohydrate
- Increased soluble fibre

No food is counted as “BAD”, but portion size is also extremely important. There should be a balanced distribution over the course of the day with regular meals and snacks.

**Insulin Treatment**

Most patients are now treated with human insulin or modified human insulins (“insulin analogues”). These are modified for more desirable properties to suit the patient. (note these still are not perfect).

They may be **short acting soluble**, or **intermediate acting NPH**; more commonly there is a combination of the above.

- **Lispro/ novorapid** - very rapid onset and short duration action
- **Glargine/ detemir** - long-acting with ‘flat’ 24h action profile

**Non-diabetic insulin profile**: in the absence of insulin, blood sugar starts to climb. You require a baseline level of insulin in order to maintain blood sugar. When you eat, there is a surge in production (3-4 hours after food) which may be 100s x higher than that of the base level. This is known as post-prandial insulin.

There are various **regimes of insulin treatment:**

- **Twice daily mixed soluble and NPH** (before breakfast + lunch) – this was used, but requires a lot more planning about times of meals, which is less practical
- **NPH long acting insulin at bedtime, and soluble insulin with meals** – this is more similar to the insulin production of a healthy individual, but requires more injections which again is not practical. However it allows patients to have more freedom with their mealtime, and the insulin can be adjusted according to meal size
  - The aim is to educate patients about how to adjust insulin levels to maintain glucose levels as close to normal. It is known as DAFNE (dose adjustment for normal eating)
- **About 20% of patients have a continuous insulin pump.** The advantage of this is that it does not require injections, and can change both long-acting and short-acting levels
  - However, there is no “closed loop” of glucose measuring and feedback, so patients must assess glycaemia using a prick test. Sub-cutaneous capillary glucose is about 20 mins behind blood glucose, so this measurement may be too late.

Current technology is a patch-pump = small wireless device which attaches to the skin and is controlled by a PDA device

**Islet cell transplants**

- This is an example of a more experimental treatment, in which donor islets are transplanted into the portal vein
- So far transplantation has been rather disappointing, because the immunosuppression required to avoid rejection is toxic for the beta cells
Assessing Treatment Success

Capillary Monitoring
In order to determine how successful treatment is, we need to monitor blood glucose levels.
  • Patients can self-monitor using a pin-prick test
  • However there are also now continuous monitors, which monitor glucose more regularly

Obviously the continuous monitors are better, but they are expensive.

HbA1c
This is an example of a long-term complication of diabetes, in which excess glucose reacts with HbA1c red cells, as it does with all proteins. This irreversible, non-covalent binding depends on:
  • The lifespan of red cells (about 120 days)
  • Rate of glycation (varies between individuals)
  • Haemoglobinopathy, renal failure etc
  • Level of glucose

HbA1c is therefore an ideal measure of long-term glycaemic control, and lower levels are associated with a lower risk of complication, particularly microvascular complication. Effectively you are measuring how much sugar is stuck to the cell

COMPLICATIONS

Ketoacidosis
A rapid decompensation of type 1 diabetes leads to hyperglycaemia and ketone production, which causes metabolic acidosis, poor tissue perfusion and dehydration
  • Incidence is from 1-8% of diabetic patients per year, with a mortality rate of 5-10%
  • DKA results from insulin deficiency, leading to:
    o reduced tissue glucose utilisation
    o increased hepatic glucose production
    o increased circulating NEFA (non-esterified fatty acids), acetoacetate and hydroxybutyrate

Hypoglycaemia
Hypoglycaemia - plasma glucose of < 3.6 mmol / l (often < 4 is used clinically)
Severe hypoglycaemia - any hypo requiring help of another person to treat
  • occasional “hypos” are inevitable as result of treating diabetes, but they are a major cause of anxiety in patients and families

Effects
  • most mental processes impaired at <3 mmol/l
  • consciousness impaired at <2 mmol/l
  • severe hypoglycaemia may contribute to arrhythmia and sudden death
  • may have long-term effects on the brain
  • recurrent hypos result in loss of warnings (therefore cannot recognise: ‘hypoglycaemia unawareness’)

Risk factors
  • Who? Patients with poor quality of glycaemic control, and low HbA1c
  • When? Pre-lunch and nocturnal hypos common, but can happen anytime
  • Why?
    • unaccustomed exercise, teens often first diagnosed after having sex
    • missed meals
    • inadequate snacks
    • alcohol
    • inappropriate insulin regime
**Signs and symptoms** of hypos are a result of:

<table>
<thead>
<tr>
<th>Increased autonomic activation</th>
<th>Impaired CNS function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palpitations/tachycardia</td>
<td>Drowsiness</td>
</tr>
<tr>
<td>Tremor</td>
<td>Confusion</td>
</tr>
<tr>
<td>Sweating</td>
<td>Altered behaviour</td>
</tr>
<tr>
<td>Pallor/cold extremities</td>
<td>Focal neurology</td>
</tr>
<tr>
<td>anxiety</td>
<td>Coma</td>
</tr>
</tbody>
</table>

**Treatment** of hypoglycaemia is both oral and parenteral, and should result in immediate recovery.

- Oral (feeding the patient) – glucose (solution or tablets), complex CHO (to maintain)
- Parenteral (given if consciousness impaired) – IV dextrose, IM glucagon
  - Concentrated solutions (eg 50% glucose) should be avoided
16. Type II Diabetes Mellitus
Dr Stephen Robinson

**Definition**
Diabetes mellitus can be defined as a *state of chronic hyperglycaemia sufficient to cause long-term damage to specific tissues, notably the retina, kidney, nerves and arteries*

- T2DM is not ketosis prone, it is not mild, and it often involves obesity, dislipidaemia and hypertension

**Diagnosis**
75g of glucose is administered orally in a glucose tolerance test.

- Below 6.0, fasted glucose is normal. Between 6.0 and 7.0, the patient has an Impaired Fasting Glucose (IFG), and above 7.0 the patient has diabetes.
- Patients with impaired glucose have increased macrovascular risk, but are not particularly likely to have increased microvascular risk (retinopathy, nephropathy) – glucose is useful in predicting macrovascular risk

**Epidemiology**

- Type 2 diabetes mellitus is the most common cause of diabetes in the world.
  - Type 1 diabetes is less common, but the least common are Maturity onset diabetes of the young (MODY) and latent autoimmune disease of adults (LADA)
- The prevalence of T2DM is increasing worldwide, with huge variation between ethnic groups
  - It is a disease of ethnicity, and of western lifestyle
- Diagnosis is also being made at younger ages; probably due to increasing obesity rates etc
- The global prevalence of T2DM is projected to double between 1995 and 2030

**Pathophysiology**

**Introduction**

- MODY is relatively uncommon, but hives useful metabolic insights into how diabetes can come about
- T2DM can be caused by genes and intrauterine environment (seen by studies using mono- and dizygous twins) and of course adult environment
- It is associated with insulin resistance and insulin secretion defects. Fatty acids are important in the pathogenesis and complications.

**MODY**
There are several hereditary forms (1-8) of MODY.
It is an autosomal dominant condition where there is ineffective pancreatic β cell insulin production; the B cells do not serve to sense ambient glucose levels correctly
It is caused by mutations of transcription factor genes and the glucokinase gene.
There is usually a positive family history, not necessarily with obesity. There is specific treatment depending on the type of diabetes.

**Mechanism of T2DM**
Twin studies have shown that T2DM appears to be a genetic disorder.

- The genes for T2DM predispose the individual to becoming obese, and obesity in turn causes insulin resistance (this may be maintained throughout adult life without developing T2DM) and β cell failure
• Intrauterine growth restriction is also linked to a predisposition for T2DM
• Obesity is not just a precipitant of t2DM, but it is also related to pathophysiology. In particular, some fatty acids exacerbate insulin resistance.
• Insulin resistance (despite not being associated with hyperglycaemia), leads to predisposition to dislipidaemia (low HDL, high LDL), hypertension and changes to various clotting factors – ie may lead to various macrovascular complications such as coronary heart disease, cerebrovascular disease and peripheral vascular disease
• Eventually insulin resistance leads to B cell failure; the patient is then unable to make sufficient insulin > worsening of dislipidaemia + hyperglycaemia > diagnosis of T2DM
• Hyperglycaemia leads to various microvascular complications, including retinopathy, nephropathy and neuropathy
• Absolute B cells failure also leads to exogenous insulin requirement

NB: T2DM has a stronger genetic basis than T1DM, despite being a disease of adulthood

**Insulin Resistance**

With increasing age...
• we make less insulin (black solid line shows this)
• we all become insulin resistant (blue dotted line)

Eventually, everyone would have T2DM

In most people these lines would intersect at the age of about 120

In some people, insulin resistance is present throughout life (exacerbated by weight), or they have a genetic predisposition to insulin resistance > lines intersected at age of about 40 = diagnosis of T2DM

**Metabolism + Presentation of T2DM**

**Presentation**

T2DM is a heterogeneous condition that usually presents with obesity, insulin resistance, insulin secretion deficit, hyperglycaemia and dislipidaemia

• The acute and chronic complications associated with diabetes such as sudden blindness, renal failure, heart attacks and stroke are also very common on presentation, as the lack of osmotic symptoms mean that patients tend not to have realized they have diabetes

**Insulin Resistance**

Blood sugar becomes high because the insulin is less effective in muscles for glucose uptake.

• Insulin secretion deteriorates with progressive impairment of glucose tolerance.
• Decreased glucose disposal and increased hepatic glucose production (output) contribute to increased plasma glucose in type 2 diabetes.
• Pancreatic islet dysfunction leads to hyperglycaemia. β cells can only compensate for insulin resistance up to a certain limit of normal glucose tolerance, after which there is impaired glucose tolerance and eventually type 2 diabetes, because with fewer β cells, α cells hypertroph and there is insufficient insulin, which causes excess glucagon and increased hepatic glucose output.

**Effect on intermediary metabolism**

Triglycerides are the main energy store of glucose. Normally, insulin prevents lipolysis (ie triglyceride breakdown)

• Insufficient/ineffective insulin > lipolysis (takes place in adipocytes), with associated glycerol and non-esterified fatty acid release
• These then go to the liver, where glycerol is used to synthesise new glucose (gluconeogenesis) and non-esterified fatty acids form VLDLs
• Glucose is then released from the liver into the bloodstream. Normally, it is taken up by muscle cells and stored as glycogen. However insufficient action of glucose reduces this uptake
• When blood glucose is sufficiently high, the patient may begin to experience osmotic symptoms
Obesity
Omental adipocytes are more important with regards to the pathophysiology of T2DM, because of their close association with the liver
- This means that waist circumference is an easy way to predict diabetes.
  - Increased waist circumference is more important than overall weight in T2DM. Central or omental obesity is more than a precipitant of diabetes. 80% of type 2 diabetics are obese.
  - Waist circumference also predicts ischaemic heart disease.
  - Above 35 inches for a woman and above 40 inches for a man increases the risk of diabetes.
- Cholesterol should ideally be under 4 for a diabetic, the normal being 5.5. Triglycerides should be 2 and HDLs should be above 1

Weight reduction is useful treatment, although unfortunately weight gain is a common side effect of diabetes treatments

Presentation
- T2DM also presents with osmotic symptoms of polyuria and polydipsia
- Patients may also be experience increased number of infections (bacteria use to glucose for energy) such as foot ulceration
- Diabetes can be picked up on early in a screening test, or later at presentation of a complication (acute could be hyperosmolar coma, chronic could be ischaemic heart disease or retinopathy suddenly going blind in one eye due to a vitreous haemorrhage).
  - Visual disturbances can also occur if the aqueous humour becomes more concentrated

Complications + Management
There are various types of complications associated with T2DM

<table>
<thead>
<tr>
<th>Microvascular</th>
<th>Macrovascular</th>
<th>Metabolic</th>
<th>Iatrogenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinopathy</td>
<td>Ischaemic heart disease</td>
<td>Lactic acidosis</td>
<td>Hypoglycaemia</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>Cerebrovascular disease</td>
<td>Hyperosmolar</td>
<td></td>
</tr>
<tr>
<td>Neuropathy</td>
<td>Renal artery stenosis</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Peripheral vascular disease</td>
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</tbody>
</table>

The basis of management of T2DM involves:
- Education
- Diet
- pharmacological treatment of glucose, blood pressure and dyslipidaemia
- complication screening

Diabetes is treated to reduce the symptoms and to reduce the chance of acute metabolic complications (although unlikely in T2DM), and also to reduce the chance of long term complications (there is a good evidence base for this). Education is essential in all of this.

Diet
Most diabetes patients are overweight, therefore dietary changes are very necessary. These include:
- Control total calories/increase exercise (weight)
- reduce refined carbohydrate (less sugar = high glycaemic index )
- increase complex carbohydrate (more rice etc, reduced glycaemic index)
- reduce fat as proportion of calories (less IR)
- increase unsaturated fat as proportion of fat (IHD)
- increase soluble fibre (longer to absorb CHO)
- Reduce salt (important for hypertension)
Treatment + Monitoring
There are 4 main aspects of T2DM which need to be treated and monitored. These include:

- **Weight**
- **Glycaemia**
- **Blood pressure**
- **Dislipidaemia**

**Weight**
Various drugs have been used to control weight.

- **Orlistat** is the one that is still available and licensed in the UK; it works by reducing fat absorption in the gut.
- **Sibutramine** has been taken off the market, but it used to work by causing the re-uptake of NA to influence central satiety in the hypothalamus and β3 thermogenesis in muscle.
- **Rimonabant** also acts on central satiety, but also causes central fat loss in adipose tissue.

**Glycaemia**
**Metformin** is the only drug in its class; a biguanide insulin sensitizer

- It is a very effective drug used commonly in an overweight patient with T2DM where diet alone has not succeeded.
- It reduces insulin resistance by reducing hepatic glucose output and by increasing peripheral glucose disposal by increasing the ability of glucose to get into muscle.
- Some GI side effects, but does not cause hypose.
- Contraindicated in severe liver, cardiac or mild renal failure

**Glibenclamide** is a sulphonurea, and works by acting on the amino acid receptor on B cells, blocking the ATP sensitive potassium channel

- This inhibition causes cell membrane depolarization, which causes voltage-dependent calcium channels to open > calcium influx > insulin release
- Usually used in lean patients with T2DM where diet alone has not succeeded
- S/E include hypoglycaemia and weight gain

**Acarbose** is an alpha glucosidase inhibitor that prolongs the absorption of oligosaccharides

- This allows insulin secretion to cope, following defective first phase insulin
- It is as effective as metformin, but side effects include flatus

**Thiazolidinediones** are peroxisome proliferator-activated receptor agonists (PPAR-gamma) such as Pioglitazine

- It is an insulin sensitizer with mainly peripheral action
- It causes adipocyte differentiation > peripheral weight gain + central weight loss
- Results in improvement in glycaemia and lipids, thus improvement in macrovascular outcomes
- Side effects may include hepatitis, heart failure

**Glucagon-like-peptide 1**
**GLP1** is a gut hormone secreted in response to nutrients in the gut

- Transcription product of proglucagon gene, mostly from L cell.
- Stimulates insulin, suppresses glucagon
- Increases satiety, therefore weight loss
- Short half life due to rapid degradation from enzyme dipeptidyl peptidase-4 (DPPG-4 inhibitor)

Other aspects of control include:

- **blood pressure** (possibly 90% of diabetics) as there are clear benefits to treatment such as a reduced chance of heart disease and stroke
- control of **diabetic dyslipidaemia** where cholesterol and triglycerides are high and HDLs are low. Again, there are clear benefits to treatment.
Screening
The problem with diabetes is the associated mortality, morbidity and cost of living with diabetes. Screening programmes are unclear in terms of specifics - which test should be done how often on who? It’s quite a difficult situation.

### DIABETES COMPARISON

<table>
<thead>
<tr>
<th>Feature</th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>0.25%</td>
<td>4-7%</td>
</tr>
<tr>
<td>Typical age</td>
<td>Child, adolescent</td>
<td>Middle-age ++</td>
</tr>
<tr>
<td>Onset</td>
<td>Acute</td>
<td>Gradual</td>
</tr>
<tr>
<td>Habitus</td>
<td>Lean</td>
<td>Often obese</td>
</tr>
<tr>
<td>Family history</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Geography</td>
<td>Europids</td>
<td>Less europids</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Usual</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Ketosis prone</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Serum insulin</td>
<td>Low or absent</td>
<td>Variable</td>
</tr>
<tr>
<td>HLA association</td>
<td>DR3, DR4</td>
<td>None</td>
</tr>
<tr>
<td>Islet B cells</td>
<td>Destroyed</td>
<td>Function</td>
</tr>
<tr>
<td>Islet cell antibodies</td>
<td>Present</td>
<td>Absent</td>
</tr>
</tbody>
</table>
17. Microvascular Complications of Diabetes Mellitus

Professor Karim Meeran

**DIABETIC RETINOPATHY**

**Imaging of the retina**

We are able to visualize both the retinal arterioles and the retina for signs of ischaemic damage using a slit lamp biomicroscope. On the **normal retina**, the optic disc and the fovea/macula should be visible

- The optic disc has no rods or cones (blind spot), but is the site where all blood vessel enter the eye
- The macula is the part of the eye responsible for sharp central vision, and is a central area comprises the highest density of cone cells

**Background diabetic retinopathy** results in the appearance of:

- **Hard exudates** (cholesterol) – appears like white bits of chalk
- **Microaneurysms** – appear like little red dots
- **Blot haemorrhages** – appear like little bits of blood

These patients will not complain of any vision changes, as the macula is functioning normally. The eye indicates a poor control of blood pressure and blood glucose, but does not suggest the patient will deteriorate to blindness.

**Pre-proliferative diabetic retinopathy** develops if the patient continues not to have good control of blood pressure and glucose. They eye appears to have:

- **Cotton wool spots** (previously called soft exudates) – this is a sign of ischaemic damage

When a cell is ischaemic, it wants more blood. The cell therefore secretes growth factors to obtain a collateral blood supply.

In the eye, new blood vessels are thin and bleed easily. Blood in the eye will cause blindness.

**Proliferative retinopathy** shows visible new vessels

- These are very thin; there is a single cell between haemoglobin and vitreous humour
- If this cell barrier tears, Hb will leak into the vitrous humour and will cause fibrosis of the vitrous which eventually causes blindness (minor vision may be maintained)

**Maculopathy** is the same as background retinopathy, except that the hard exudates are present near the macula

- This might threaten direct vision, and central vision may be lost quite early on

**Management of diabetic retinopathy**

After taking a detailed history and examination of the eye, a management plan must be developed (depends on the stage of retinopathy development)

- **Background retinopathy**
  - Improve control of blood glucose
Warn patients that warning signs are present, and that ignoring advice may cause worsening and impaired vision

- **Pre-proliferative retinopathy** suggests general ischaemia; if left alone this will result in neovascularization of the eye
  - The patient therefore needs pan retinal photocoagulation
  - In PRP, we sacrifice a 1/3 of the peripheral vision using a lazer (infracting the tissue), thus we reduce the demand on the retina for oxygen and preserve central vision

- **Proliferative retinopathy** also requires pan retinal photocoagulation
- **Maculopathy** only requires a grid of photocoagulation, in which leaky vessels surrounding the macula are sealed off

**DIABETIC NEPHROPATHY**

**Clinical importance:** The clinical hallmark of diabetic nephropathy is proteinuria, and this is associated with cardiovascular morbidity

- This associated morbidity and mortality poses a healthcare burden
- Treatment options are present

**Histological Features**

These can be divided into those that are glomerular, vascular and tubulointerstitial.

**Glomerular Changes**

- Mesangial expansion (specialized smooth muscle cells that function to regulate blood flow through the capillaries)
- Basement membrane thickening
- Glomerulosclerosis (hardening)

**Vascular**

**Tubulointerstitial**

NB: in diabetic nephropathy, there is an overlap between metabolic and haemodynamic causes (not explored in great detail)

- Essentially, there is over production of matrix leading to mesangial expansion and to basement membrane thickening. As this progresses you get sclerosis of the glomerulus and secondary effects in the tubulointerstitium.
- The stimuli for the development of these processes are multiple and include effects of prolonged exposure to high glucose or glycosylated proteins in at risk patients (ie there is a probable genetic factor or factors). In addition rise in the pressure within the glomerular "capillaries" (they are really arterioles) can stimulate a similar expansion of matrix.
- Angiotensin has many bad effects which include stimulation of pathways of matrix over production. Angiotensin also results in constriction of the efferent arteriole which is greater than the afferent arteriole leading to a rise in the trans glomerular capillary pressure. This is termed the haemodynamic mechanism for glomerulo sclerosis and was the original basis for the use of ACE inhibitors and Ag Receptor blockers in patients with diabetic nephrtopathy.
Epidemiology
There is a changing epidemiology with regards to diabetes and diabetic nephropathy
  • The proportion of patients that develop nephropathy after 30 years is probably equal in both T1DM and T2DM
  • However there is a world epidemic in T2DM
In type 2 diabetes, epidemiological factors to consider include:
  • Racial Factors, ie afro-carabs, asian, chinese (everyone but caucasians)
  • Age at presentation has been decreasing due to increased teenage obesity

Clinical Features
The development of diabetic nephropathy is over a period of years, and the course of disease is key to understanding clinical features:
  • Progressive proteinuria
  • Increased BP
  • Deranged renal function

Proteinuria gradually increases, and requires frequent recordings to monitor development
  • Normal Range <30mg/24hrs
  • Microalbuminuric Range 30 - 300mg/24hrs
  • Asymptomatic Range 300 - 3000mg/24hrs
  • Nephrotic Range >3000mg/24hr

Increased BP
  • In healthy patients, there are normal subtle changes that occur in blood pressure during the day, for example the nighttime dip
  • In diabetics, the overall blood pressure is increased slightly, and this nighttime BP dip is often lost

Intervention
If good strategies for intervention are developed and instigated, most patients can be stabilized + converged into a chronic disease

Glucose control
  • Intensive glucose control has been shown to significantly reduce the percent of patients who go on to develop diabetic nephropathy
  • This reduction is most significant in patients who have suffered for >5 years

Hb1Ac
  • Lowering mean Hb1Ac has also been shown to lower the risk of nephropathy
  • A 37% decrease in risk was shown per 1% decrement in Hb1Ac

Blood pressure may be controlled by ACE inhibitors or Ang II blockers
  • One of the effects of Ang II is to tighten the efferent arteriole supplying the glomerulus
    o This leads to an increase in glomerular capillary pressure
    o Relief of this efferent vasoconstriction will reduce this pressure, and thus risk of nephropathy
  • ACE inhibitors have been show to reduce the production of proteinuria
    o Also reduction in cardiovascular morbidity

In summary, the strategies for intervention should include:
  • Diabetic control
  • Blood pressure control
  • Inhibition of the activity of the RAS system
  • Stop smoking
DIABETIC NEUROPATHY

Neuropathy results from the blocking of the vasa nervorum (small blood vessels supplying nerves). There are different types of diabetic neuropathy, each requiring slightly different treatment:

- Peripheral polyneuropathy – affecting the PNS
- Mononeuropathy – only affecting a single nerve
- Mononeuritis multiplex – damage to at least two distinct nerve areas
- Radiculopathy – affecting nerve root
- Autonomic neuropathy – affecting autonomic nerves
- Diabetic amyotrophy (only reversible cause) – affects lower limbs

Mechanism of blood vessel damage

The mechanism of blood vessel damage is unknown, but there are a few hypotheses:

- It is thought that high levels may be converted to sorbitol (alcohol) by aldose reductase, and sorbitol is responsible for vessel damage
- Another possible mechanism is the production of advanced glycation end products (AGE)
  - Glycation is the term used for non-enzymatic addition of hexoses to protein, whereas glycosylation is the term used for enzymatic addition
  - Glycation of hemoglobin to form Hb1Ac is well recognized, and a similar process is known to affect other proteins, in particular the lens protein (cataracts), fibrin and collagen in vessel wall
  - Fructosamine is another example of a glycated protein. We can use both Hb1Ac and fructosamine to get an idea of long term glucose control

Types of Neuropathy

Peripheral neuropathy

- Affects longest nerves supplying feet
- Usually bilateral and symmetrical, loss of sensation of common but can be painful
- Occurs more commonly in tall people and those with poor glucose control
- This can be dangerous as people may become unaware of foot injury
- Signs include:
  - Loss of ankle jerks
  - Loss of vibration sense (test using tuning fork)
  - Charcot's joints (multiple small fractures on foot)

Mononeuropathy

- Sudden single motor nerve
- This may present as wrist drop or foot drop
- Also may present as cranial nerve palsy (3rd, 4th or 6th)
  - 3rd nerve palsy results in double vision (diplopia)
  - pupil sparing 3rd nerve palsy is common – eye is usually “down and out” (6th nerve pulls out, 4th pulls down), but the pupil still responds to light
    - parasymptathetic fibres tend to lie on the outside of the nerve, and have a separate blood supply therefore are not usually affected
    - in contrast, a 3rd nerve palsy caused by an aneurysm (space occupying lesion, surgery) is different. The aneurysm presses on the parasymptathetic fibres first > fix dilated pupil

Mononeuritis multiplex is a random combination of peripheral nerve lesions

Radiculopathy is pain over spinal nerves, usually affecting a dermatome on the chest wall or abdomen

Autonomic neuropathy results from loss of sympathetic and parasymptathetic nerves to GI tract, bladder and cardiovascular system
• GI tract effects: difficulty swallowing, delayed gastric emptying, constipation with nocturnal diarrhoea (bacterial overgrowth resulting from stool stasis)
• Bladder dysfunction
• Postural hypotension
• Cardiac autonomic supply affected, therefore reports of sudden cardiac death
• Diagnosis:
  o Measure changes in heart rate in response to Valsalva manoeuvre (moderately forceful attempted exhalation against a closed airway, usually done by closing one’s mouth and pinching one’s nose shut.)
  o This should result in a change in heart rate (look at R-R intervals)

**Diabetic amyotrophy**
• Assymetric painful proximal motor loss
• Affects quads and lower limbs, and causes wasting
18. The pathophysiology of diabetic ketoacidosis

Dr Andrew Frankel

T1DM = organ specific autoimmune disease > deficient insulin production
DKA occurs when there is a profound and life-threatening deficiency in insulin. There are various causes of this. Precipitants include:
- Infection
- New diagnosis
- No cause
- No insulin
- Ischaemic event
- Other

**PATHOPHYSIOLOGY**

**Insulin deficiency** causes high HGO and deficient muscle glucose uptake
High plasma glucose > glucose exceeds PCT ability for reabsorption

**Basic mechanism**
- Insulin deficiency + stress hormones > hyperglycaemia
  - Hyperglycaemia > osmotic diuresis > dehydration (when cant drink enough or vomiting)
    - Fever may worsen this dehydration
- Insulin deficiency + stress hormones (+ fasting) > ketosis

When **insulin is low**, there is:
- Increased lipolysis
- Glycerol is used to produce glucose in the liver
- Fatty acids are used to produce ketone bodies in the liver

Nb: Urinary **ketones** could occur in a non-diabetic, ketone production occurs with insulin deficiency + ketones are produced from fatty acids. In the absence of food, ketone production is used to protect glucose delivery to the brain, at the expense of everything else.

**Metabolism** is finely balanced between maintaining blood sugars. In the absence of this balance, we find that the production of glucose via liver + production of ketone bodies start to dominate.

**Acid-Base balance**: bicarbonate production is linked to H+ excretion.
- In the DCT, adequate glomerular filtration for function, carbonate dehydratase is important for acid base homeostasis, Na, H + K excretion are linked, acid ketone bodies require bicarbonate buffering
- **Bicarbonate generation** by the kidney: Na+ transport does not happen independently, therefore if you want to excrete H+, you need to hold onto Na.
- One of the ways that DKA presents i= shortness of breath, ie want to reverse process
- **Metabolic acidosis** = decreased pH, decreased HCO3 and decreased co2 (compensation)

**Reduction in bicarbonate** because of impaired production + increased hydrogen buffering > metabolic acidosis
- Metabolic acidosis can occur because of an addition of acid (ketones, lactate etc) to the blood stream, or due to changes to bicarbonate, chloride

Calculating **anion gap** = difference between anions and cations
- Normally, we are isoelectric
• If we are have a high anion gap = more acids
  Normal anion gap = due to cations
**Electrolytes disturbances** are caused by:
- Water loss in urine
- Sodium loss in urine
- Potassium loss in urine, although high K in blood test but low total

**Back to mechanism**
Ketosis > acidosis > hyperventilation + vomiting > dehydration > renal hypoprofusion > impaired H+ excretion > more acidosis

**CLINICAL INFORMATION**

**Clinical features:**
- Dehydration
- Insulin deficiency
- Totally body potassium deficiency
- High plasma potassium
- Acidosis
- Risk of arrhythmia, infection, dilated stomach
- Polyuria + polydipsia
- Dehydration
- Hyperventilation
- Abdominal pain and vomiting
- Coma
- **LOOK FOR PRECIPITATING FACTOR**
- glycosuria + ketonuria

**Investigations**
- Capillary glucose
- Plasma glucose
- U+E: Creatinine, K+, Na+
- FBC
- Arterial blood gases
- Amylase
- X-ray

**Treatment:**
- Fluid (immediate; 1 litre of saline in 30 mins)
- Insulin (long-term; given IV sliding scale with capillary glucose)
- Potassium (replacement)
- Bicarbonate (controversial)
- Other measures
19. Macrovascular Complications of Diabetes
Dr Nick Oliver

This lecture addresses key concepts revolving around macrovascular complications of Diabetes.

Concept 1: Hyperglycaemia is part of a spectrum of arterial disease that significantly reduces life expectancy

High glucose (>6 mmol/l fasting) itself does not cause macrovascular disease, but when in associated with other factors it significantly contributes. These factors include:
- Waist circumference
  - Men > 102 cm
  - Women > 88 cm
- HDL
  - Men < 1.0
  - Women < 1.3
- Hypertension (BP > 135/80)
- Microalbumin
- Insulin resistance

Diabetes has a huge impact of life-expectancy; early diagnosis significantly reduces life expectancy. Most of this mortality is attributed the macrovascular complications.
- TSDM patients often have high insulin levels to overcome resistance, and this again increases the risk of having a major CHD event
- The relative risk of cardiovascular events in people without diabetes is 1.0. However with diabetes this risk increases to between 3 and 8 (depending on the type of CV event)
- When comparing conventional with intensive therapeutic agents, we see that over time, Hb1Ac increases regardless of intervention. This is because all of tend towards diabetes with ageing. Hb1Ac is also associated with increased risk of MI

Concept 2: Patients with Diabetes die from diseases of big arteries

Evidence
- CVD and IHD account for >75% of deaths in diabetics, compared to only about 50% in the general population
- People with diabetes have the same relative risk of a MI as non-diabetics who have had a prior MI. This shows that not only do diabetics clearly have coronary artery disease, but they require aggressive risk management
- Cardiovascular mortality increases with age. However this increase is much greater in diabetics than in the general population
- The risk of death among MI survivors is 40% higher in diabetics

NB: there are ethnic differences in the prevalence of diabetes; higher in people of black or Asian origin at all age groups

Concept 3: Macrovascular Disease is a systemic disease and is commonly present in multiple arterial beds

So far we have addressed data concerning diabetes and MI, CHD, IHD etc, but it is not only the coronary arteries that are affected.
- Cerebrovascular disease has an earlier onset in diabetics compared to non-diabetics, and is more widespread.
  - Ischaemic strokes are more prevalent among diabetics
- Peripheral vascular disease is also very common, and this contributes to diabetic foot problems with neuropathy (see microvascular complications lecture)
- Renal artery stenosis is common amongst diabetics, and may contribute to hypertension in some
Concept 4: Treatment targeted to blood glucose alone does not significantly offset the increased risk of cardiovascular disease

Intensive glucose control has been shown not to have an impact on improvement of CHD risk in T2DM, and in fact results in an increased risk of mortality.

Concept 5: Prevention of macrovascular disease requires aggressive management of multiple risk factors

Risk factors for macrovascular disease may be described as non-modifiable or modifiable
- Non-modifiable: age, sex, birth weight, FH, genes
- Modifiable: dislipidaemia, hypertension, smoking, diabetes

Intervention
- Statins can be used as a treatment to target dislipidaemia; they reduce total and LDL cholesterol, and the primary outcome shows a risk reduction in CV events by 37%
- Aggressive blood pressure treatment is also important in reducing both MI and microvascular risks
- There are various blood glucose lowering therapies, including metformin, sulphonylurea etc (see T2DM lecture notes)

NB: Glycated Haemoglobin (HbA1c): the non-enzymatic adduction of glucose or glucose-derived products to normal HbA is associated with increased risk of macrovascular complications

Blood pressure management

Targets
- If kidney, eye or cerebrovascular damage, set a target < 130/80 mmHg.
- Others, set a target < 140/80 mmHg.

If on antihypertensive therapy at diagnosis of diabetes
- Review BP control and medication use.
- Make changes only if BP is poorly controlled or current medications are inappropriate because of microvascular complications or metabolic problems.

If the person’s BP reaches and consistently remains at the target
- Monitor every 4–6 months and check for possible adverse effects of antihypertensive therapy (including those from unnecessarily low blood pressure).

Management of blood lipids

Review CV risk status annually:
- assess risk factors, including features of metabolic syndrome and waist circumference
- note changes in personal or family CV history
- perform full lipid profile (including HDL-C and TG) – also perform after diagnosis and repeat before starting lipid-modifying therapy.

If history of elevated serum TG, perform full fasting lipid profile (including HDL-C and TG).

Consider to be at high CV risk unless all of the following apply:
- not overweight (tailor with body-weight-associated risk assessment according to ethnic group)
- normotensive (< 140/80 mmHg in absence of antihypertensive therapy)
- no microalbuminuria
- non-smoker
- no high-risk lipid profile
- no history of CV disease
- no family history of CV disease

Estimate CV risk from UKPDS risk engine annually if assessed as not at high CV risk (see www.dtu.ox.ac.uk/index.php?maindoc=riskengine/).
20. The Diabetic Foot
Nick Oliver

**EPIDEMIOLOGY + IMPORTANCE**

**Predisposition**
Complications of DM predisposing to foot disease:
- Neuropathy
- Peripheral vascular disease

**Epidemiology**
- Prevalence in UK = 2-3%
- Current or past foot ulcers in DM = 5-7%
- Risk of amputation 60x in diabetics
- Poor prognosis following amputation
- 10% of NHS bed occupancy due to diabetic-related problems

**PATHOGENESIS**

**Indications**
- Clawing/curling toes, start of ulcer from rubbing on shoe
- Thickening in the soft tissue/tendons in the hands
- Dry skin over feet, which may crack > ulceration
- Exaggerated arch (PEZ) – plantar flex (loss of innervation to muscle fibres, therefore stronger muscles move toes up).

**Pathway to foot ulceration:**
There are different contributing factors which may lead to/cause diabetic foot disease.
- Motor neuropathy
- Limited joint neuropathy
- Autonomic neuropathy
- Trauma
- Sensory neuropathy
- Peripheral vascular disease
- Reduced resistance to infection
- Other diabetic complications

**Foot ulceration**
- **Neuropathic** foot = numb, warm, dry, palpable foot pulses, ulcers at point of high pressure
- **Ischaemic** foot = cold, pulseless, ulcers at foot margins
- **Neuro-ischaemic** foot = numb, cold, dry, pulseless, ulcers at point of high pressure + foot margins

Assessment of the foot
- **Appearance** – deformity, callus
- **Feel** – hot/cold, dry
- Foot pulses – dorsalis pedis (top of foot), posterior tibial (on ankle)
- Neuropathy – vibration sensation, temperature, ankle jerk reflex, fine touch sensation

**PREVENTATIVE + TREATMENT STRATEGIES**

**Management (Preventative)**
- There are different aspects of management, targeting:
  - Hyperglycaemia
  - Hypertension
- Dislipidaemia
- Smoking
- Education

Special foot care: inspect feet daily, measure feet when buying shoes, buy square shoes with laces, inspect inset of shoes for foreign objects, attend chiropodist, cut nails straight across, care with heat, never walk barefoot

**Management (of ulceration)**

**MDT**
- Diabetologist
- Nurse
- Chiropodist
- Vascular surgeon
- Orthopaedic surgeon
- Orthotist
- Limb fitting centre

**Other**
- Relief of pressure – bed rest, redistribution of pressure
- Antibiotics
- Debridement
- Revascularization – angioplasty, arterial bypass surgery
- Amputation

**NB:** Sharkoneuropathy – not every diabetic foot is an ulcer or infection. Loss of nerve supply > abnormal walking > eroding of bones etc > rock bottom foot.