## Endocrinology

### PITUITARY AND HYPOTHALAMIC DISORDERS

#### General Principles

The **hypothalamus** and **pituitary glands** have important roles in the control of the endocrine system. The pituitary gland consists of two parts (anterior and posterior) which have different embryological origins and functions.

1. **Anterior pituitary** is derived from an outgrowth of the primitive pharynx (Rathke’s pouch) and synthesises hormones that stimulate other endocrine glands or act on target tissues
   a. Synthesis is controlled by inhibitory (prolactin) or stimulatory (everything else) factors from the hypothalamus, depending on metabolic, physical, humoral and nervous input
   b. Adrenocorticotrophic hormone (ACTH), thyroid-stimulating hormone (TSH), luteinising hormone (LH), follicle-stimulating hormone (FSH), growth hormone (GH) and prolactin (PRL)

2. **Posterior pituitary** is derived from nuclei arising from the supraoptic and paraventricular nuclei of the hypothalamus; its main function is storage of vasopressin and oxytocin from the hypothalamus

#### Hypopituitarism

**Hypopituitarism** is a generalised condition caused by partial or total failure of the pituitary hormones. It is most often due to pituitary tumours, but may be congenital. Incidence is ~3 per 100,000, and it is associated with a 1.8-fold increased risk of early death from cardiovascular, respiratory and cerebrovascular disease.

1. **Aetiology:**
   a. Tumours or 2° to treatment – pituitary, hypothalamic, parasellar (meningioma), metastatic
   b. Pituitary apoplexy – haemorrhage 2° to anticoagulation, DM, Sheehan syndrome, ischaemia
   c. Infiltration – sarcoidosis, histiocytosis, Wegener granulomatosis, TB, haemochromatosis
   d. Genetic – mutations in Pit-1 or Prop-1 transcription factors
   e. Others – empty sella (arachnoid herniation), trauma (basilar skull fracture), ICA aneurysm, isolated tropic defect (Kallman syndrome – failure of LHRH secreting neurons to migrate)

2. **Clinical features:**
   a. Symptoms – tiredness, weight loss (central obesity 2° to ↓GH), anorexia, dizziness, hypothyroid symptoms, hypogonadal symptoms
   b. Signs – pallor, hypogonadal features (purse-string sign – lines around mouth, thin skin, genital atrophy, loss of 2° sexual characteristics), skin atrophy, postural hypotension (ACTH)
   c. Investigations – anaemia (normochromic normocytic), ↓Na⁺, ↓T4 and TSH (not sensitive or specific – may actually be normal due to immunologically but not biologically active TSH)

3. **Management:**
   a. Treatment is as for individual hormone deficiencies, but the order of initiation is important – glucocorticoids (vasopressin) → thyroid hormones → gonadotropins → growth hormone
   b. Patients with ACTH deficiency may need additional cortisone during times of major physical stress (e.g. fever >38.3°C or acute illness)

#### Pituitary tumours

Are usually benign tumours derived from secretory cells – prolactinomas (35%), GH-secreting tumours (15%), corticotropin secreting tumours (10%) and others (10%; gonadotropins, TSH and subunits). Note that 30% of pituitary tumours are non-secreting.

1. **Classification:**
   a. Size – macroadenomas (>1cm diameter), microadenomas (<1cm diameter)
   b. Staining – chromophobic (prolactinomas), eosinophilic (acromegaly), basophilic (Cushing)

2. **Clinical features:**
   a. Mass effects – visual fields (bitemporal hemianopia), optic nerve pressure, cavernous sinus infiltration, hypothalamic pressure, cranial pressure/hydrocephalus, hypopituitarism
   b. Hormone excess – prolactin (galactorrhoea, amenorrhoea; impotence), growth hormone (acromegaly), ACTH (Cushing disease), TSH (rare), gonadotropins and subunits (rare)
   c. Investigations – hormone radioimmunoassay, CT or MRI visualisation of lesion (note that about 10% of asymptomatic adults have pituitary masses by MRI)

3. **Management** – multimodality usually required for best results
   a. Transphenoidal (stereotactic) surgery
   b. Radiation therapy for recurrent tumours and for patients who do not undergo surgery; leads to 80-100% regression when used in conjunction with surgery
   c. Hormone suppression – somatostatin analogues, dopamine agonists, receptor blockers

#### Prolactinoma

Is the most common type of pituitary tumour.

1. **Differential diagnosis of raised serum prolactin:**
   a. Physiological stimuli – stress, lactation, breast stimulation
   b. Medication – OCP, withdrawal of OCP (post-pill amenorrhoea), psychotropic agents
   c. Abnormal neuroendocrine control – idiopathic hyperprolactinaemia
Endocrinology

2. Clinical features:
   a. May be asymptomatic or present with amenorrhea, galactorrhoea (prominent Montgomery tubercles), infertility (hypogonadism in males) or osteoporosis (oestrogen suppression)
   b. 3 or more measurements of PRL levels are required as secretion is pulsatile; levels >20,000 are almost always due to a large macro-prolactinoma, while lesser elevations may be due to micro-prolactinomas, idiopathic neuroendocrine disorders or stalk/hypothalamic pressure
   c. If prolactin is raised without other reasons, pituitary scanning (CT/MRI) is needed to exclude a non-hormone secreting pituitary adenoma causing stalk pressure.

3. Management
   a. Dopamine agonists may be required for >18 months – bromocriptine 2.5mg po bd or cabergoline 0.25mg twice a week (D2 selective, more effective and better tolerated)
   b. Surgery – >70% microadenomas have complete response; macroadenomas have 32% initial cure and 19% recurrence rate (though debulking may still be done)
   c. Radiotherapy is used for large invasive macroadenomas which fail medical shrinkage, but is rarely used for prolactinomas as medical therapy is usually sufficient

Acromegaly is usually due to a GH-secreting pituitary adenoma (GH stimulates somatomedin production, which stimulate growth of soft tissue structures); other causes include hypothalamic tumours (overproduction of GHRH) and ectopic production of GH.

1. Clinical features – characterised by growth of hands, feet and head with coarsened facial features and frontal bossing (increased spacing between teeth)
   a. Other symptoms – visual field defects, fatigue, headaches, weight gain, decreased libido, erectile dysfunction, oligomenorrhoea, weakness, proximal myopathy, hyperglycaemia, carpal tunnel syndrome, diaphoresis, heat intolerance, heart failure, seizures
   b. Complications – congestive heart failure, nephro lithiasis and nephromegaly, pituitary apoplexy, diabetes mellitus, cholestasis (70%), osteoarthritis and disfigurement
   c. Investigations – high and non-glucose suppressible GH levels and raised serum IGF-1 levels (good specificity but lower sensitivity; not reliable in nephrotic syndrome); GHRH levels, MRI

2. Management
   a. Surgery – 60% of microadenomas and 30-40% of macroadenomas cured based on normalisation of serum hormone levels, though more may achieve a ‘safe’ serum GH level
   b. Radiotherapy – used as an adjunct to surgery or in patients in whom surgery cannot be done; reduction in GH levels may take years if used as primary therapy
   c. Medical – dopamine agonists (suppress GH levels in acromegaly; stimulate GH in normal persons), octeotride (blocks GH release from somatotrophs), GH receptor antagonists

Hypotalamic Disorders

Hypothalamic disorders may be due to craniopharyngiomas, dysgerminomas, upward pressure from pituitary adenomas, gliomas, infiltration (sarcoïd, histiocytosis X, haemochromatosis, TB), metastasis or 2° to radiation (e.g. radiotherapy for pituitary adenoma). Clinical features include hypopituitarism, obesity, somnolence, diabetes insipidus, thirst defects, hydrocephalus and rarely anorexia (lesion in feeding centre).

Diabetes insipidus is due to failure of vasopressin (anti-diuretic hormone), which normally acts on the renal collecting ducts to increase water resorption.

1. Classification – partial or complete; central or nephrogenic
   a. Central due to failure of production 2° to hypothalamic and/or pituitary damage – pituitary tumours, granulomatous diseases, post-traumatic, surgery, Guillain-Barre syndrome, aneuerysm, drug-induced (ethanol, phenytoin), autoimmune polyendocrinopathy, idiopathic
   b. Nephrogenic due to failure of collecting duct to sense ADH – congenital or acquired (renal disease, hypercalcaemia, hypokalaemia, drugs – lithium, amphotericin, methoxyflurane)

2. Clinical features:
   a. Symptoms include polyuria (3-10L/day), polydipsia, dehydration, hypernatraemia
   b. Investigations – hypernatraemia, plasma osmolality >2.4 times serum osmolality (overnight water deprivation test), arginine ADH challenge to distinguish central diabetes insipidus

3. Treatment:
   a. Central – DDAVP (desmopressin) or aqueous vasopressin nasal spray
   b. Nephrogenic – thiazide diuretics, amiloride, prostaglandin inhibitors; treat ↓K⁺ and ↓Ca⁺

ADRENAL DISORDERS

• General Principles

The adrenal glands lie in the retroperitoneal space adherent to the upper poles of the kidneys.
Endocrinology

1. Adrenal medulla develops from ectodermal neural crest tissue and receives preganglionic cholinergic nerve fibres from sympathetic nerves.
   a. Secretion of catecholamines, adrenaline and noradrenaline occurs in response to a variety of stimuli such as exercise, emotion, surgical trauma, hypoglycaemia and fear
   b. Actions are mediated through alpha and beta adrenergic receptors – adrenaline binds to both types of receptors, while noradrenaline has predominantly alpha adrenergic effects
2. Adrenal cortex arises from mesoderm and is divided into the zona glomerulosa (aldosterone) and the zona fasciculata and reticularis (glucocorticoids, androgens and oestrogens)
   a. Mineralocorticoids – aldosterone (acts on the distal renal tubule to promote potassium excretion and sodium uptake); controlled by the renin-angiotensin system
      i. Renin secreted (2° to low intravascular volume, cardiac failure, hypoalbuminemia and sodium depletion) acts on hepatic angiotensinogen to produce angiotensin I
      ii. Angiotensin I is converted by pulmonary ACE to angiotensin II, which has a direct vasoconstrictor action and also stimulates aldosterone production
   b. Glucocorticoids – cortisol (stimulates protein synthesis); stimulated by ACTH released in a diurnal rhythm (high in the morning, low in the evening) or due to stressful stimuli
      i. ACTH is under the control of corticotrophin releasing factor, and receives feedback control by cortisol

Exogenous steroids vary in their potency and their mineralocorticoid/glucocorticoid potency.
1. Dose adjustment:
   a. Hydrocortisone is 1:1 in terms of GC and MC action; 25mg is a replacement dose for both
   b. Prednisone is 5:1 in terms of GC and MC action; 5mg is the GC replacement dose
   c. Dexamethasone is 50:0 in terms of GC and MC action; 0.5mg is the GC replacement dose
   d. Fludrocortisone is 0:125 in terms of GC and MC action; 0.2mg is the MC replacement dose
2. Adverse effects are numerous:
   a. CVS – hypertension
   b. GIT – gastric ulcers, pancreatitis
   c. CNS – cataracts, proximal myopathy, intracranial hypertension, psychosis
   d. Bone – osteoporosis, aseptic necrosis
   e. Endocrine – diabetes, hypokalaemia, obesity
   f. Renal – salt and water retention
   g. Immune – suppression → sepsis, TB
   h. Skin – purpura, thinning, striae, poor healing
3. Advice for chronic steroid use:
   a. General – life-long treatment, steroid card/bracelet, IMI hydrocortisone PRN
   b. Illness – if unwell, take 3x dose (better over treated as vomiting → viscous cycle requiring parenteral HC to break); major illness may also need HC 50-100mg tds po/iv until resolved
   c. Withdrawal – 2-3 weeks no problem, >5-6 weeks taper over 2 weeks, >5 years forget about it

Adrenal Disorders

Investigations for adrenal disorders:

1. Cortisol:
   a. Excess – 24 hour urinary free cortisol, 1mg overnight dexamethasone suppression test
   b. Insufficiency:
      i. Primary – 1 µg short Synacthen test, basal ACTH
      ii. Secondary - 1 µg short Synacthen test, metyrapone test, ITT

2. Catecholamines:
   a. Excess – 24 hour urinary adrenaline and noradrenaline
   b. Insufficiency – clonidine suppression test

3. Aldosterone:
   a. Excess – ambulant plasma aldosterone-to-renin ratio
   b. Insufficiency – renin (↑), aldosterone (↓), serum potassium (↑)

4. Androgens:
   a. Excess – plasma DHEAS, testosterone (women)
   b. Insufficiency – basal and ACTH-stimulated 17-OH-progesterone (CAH)

Primary adrenal insufficiency usually affects aldosterone, cortisol and sex steroid production. Adrenal medulla production of vasoactive amines may be normal or compromised – in true autoimmune adrenal destruction this is generally spared.
1. Aetiology:
   a. Congenital – congenital lipoid adrenal hyperplasia, congenital adrenal hyperplasia
   b. Autoimmune – Addison disease, polyendocrine failure, anti-adrenal antibodies, HLA-DR3
Endocrinology

c. Adrenal haemorrhage – coagulopathy, post-operative, anti-coagulation, cardiac disease, infection (meningococcal), post-partum septicaemia (Waterhouse-Friedrickson syndrome)
d. Infiltration – tuberculosis, metastatic disease

2. Clinical features:
a. Weakness and fatigue (100%), weight loss (100%), hyperpigmentation (92%, doesn’t occur in 2nd failure), hypotension (88%), hyperkalaemia (64%), gastrointestinal symptoms (56%)
b. Others – postural dizziness, presyncope, syncope, hypercalcaemia, muscle and joint pain, vitiligo, eosinophilia, reduced libido, increased anxiety
c. Investigations – very low cortisol or decreased response to ACTH (↑), ↑K+, ↓Na+, ↑creatinine; adrenal antibodies (Addison), CT adrenal, CXR and Mantoux status

3. Management:
a. Glucocorticoid – hydrocortisone 20-25mg/d in 2-3 divided doses or prednisone 4-5mg/d
b. Mineralocorticoid – fludrocortisone 0.05-0.2mg/d, beware underdosing (orthostasis, ↑K+)

Primary hyperaldosteronism causes Na+ resorption and K+ loss, which causes volume expansion – while this leads to reduced renin and subsequently lower angiotensin II, this negative feedback is insufficient. In pseudoaldosteronism (Liddle syndrome) there are activating mutations of amiloride-sensitive Na+ channels also leading to increased salt absorption and K+ loss.

1. Aetiology:
a. Adrenal mass – ‘incidentaloma’, benign adenoma, carcinoma (<2%)
b. Adrenal hyperplasia
c. Idiopathic hyperaldosteronism – normal glands, ectopic aldosterone secretion (uncommon)
d. Glucocorticoid remediable aldosteronism

2. Clinical features:
a. May present with incidental or diuretic-induced hypokalaemia, refractory hypertension, family history of primary aldosteronism/hypertension or early-onset hypertension
b. Symptoms include those of hypokalaemia (muscle fatigue, cardiac arrhythmias especially bradycardia, prominent U waves on ECG), hypertension, weight gain, oedema
c. Investigations – aldosterone-to-renin ratio >20-30 and aldosterone >600pmol/L, saline infusion (normally → renin and aldosterone suppression), urinary K+ >30mmol/L, CT/MRI
   i. High aldosterone, low renin – Conn syndrome (1st aldosterone-secreting tumour)
   ii. High aldosterone, high renin – renal artery stenosis
   iii. (Low aldosterone, low renin – hyporenininaemic hypoaldosteronism (↑K+))

3. Management:
a. Adenoma → surgery
b. Hyperplasia → medical therapy (spironolactone + ACE inhibitors for hypertension)

Phaeochromocytomas are rare. The 10% rule is handy – 10% are extra-adrenal (10% extra-abdominal), 10% are bilateral, 10% are adenalin-secreting, 10% are malignant, 10% are familial and 25% are syndromic with mutations of RET, VHL, SDHB or SDHD genes. There is increased incidence in MEN-2a and 2b, Von-Hippel-Lindau disease, neurofibromatosis type 1 and some isolated autosomal dominant conditions.

1. Clinical features – usually presents around 42 years of age with paroxysms of symptoms and signs
   a. Symptoms – severe headache, perspiration, palpitations, tachycardia, anxiety, tremulousness, chest and abdominal pain, nausea and vomiting, weakness, fatigue, weight loss, dyspnoea, heat intolerance, visual disturbance, dizziness/faintness, constipation
   b. Signs – hypertension sustained (65%) or paroxysmal (25%) or gestational (4%), pallor
   c. Investigations – elevated plasma catecholamines or metanephrines (metabolites), 24-hour urinary catecholamines (2-3x elevated), clonidine suppression or glucagon stimulation test
d. Localisation – MRI>CT (bright on T2), MIBG isotopic scan, PET scan, venous sampling

2. Management:
a. Hypertensive crisis – nitroprusside, labetolol, phenolamine (alpha blockade)
b. Alpha blockers for 2-3 weeks to deplete catecholamines, beta blockers to prevent reflex tachycardia from alpha blockers, maintain intravascular volume then surgical resection

Adrenal incidentalomas are found on 1-2% of abdominal CT scans and 2-10% at autopsy (increased prevalence with age). 1-7% are carcinomas, but even if there is known malignancy >50% are benign. 10% are associated with cortisol autonomy, 3% are phaeochromocytomas and 1% are aldosterone secreting.

1. Smooth, homogenous favours adenoma
2. Density – high fat favours adenoma, loss of signal on out-of-phase MRI favours adenoma
3. Size – <4cm favours adenoma, no carcinoma >5cm, size stability over time favours adenoma
Endocrinology

Cushing Syndrome

Cushing syndrome is the term used to describe the effects of cortisol excess and may be due to exogenous administration of corticosteroids or may result from endogenous hypercortisolism e.g. cortisol secretion from an adrenal adenoma (Cushing disease).

1. Aetiology:
   a. Corticotropin dependent – pituitary adenoma (70%) or carcinoma, ectopic ACTH production (small cell lung cancer), carcinoids, ectopic CRH, bilateral adrenal hyperplasia, iatrogenic
   b. Corticotropin independent – adrenal adenoma, adrenal hyperplasia, adrenal carcinoma, Carney complex (primary pigmented nodular adrenocortical disease)
   c. Pseudo-Cushing syndrome – major depression, alcoholism – long term, active alcoholism and withdrawal from EtOH intoxication
   d. Miscellaneous – physiological stress (surgery, severe illness), anorexia and bulimia, glucocorticoid receptor resistance, severe obesity

2. Clinical features:
   a. Presentation variable – depression, hypomania, ‘spot’ diagnosis, diabetes, hirsutism, amenorrhoea, osteoporosis, fractures, hypertension
   b. Symptoms – weight gain, hyperglycaemia, buffalo hump, abdominal striae, ↑BP, poor sleep, depression, oedema, osteopenia, hirsutism, recurrent infections, poor wound healing
   c. Investigations – screening (raised urinary cortisol or non-suppression to <135nmol/L after overnight dexamethasone 1mg), then definitive testing to demonstrate non-suppressability of serum and/or urine cortisol, then tests to identify the site of lesion (MRI, CT, scintigraphy)

3. Management:
   a. Adrenal – adrenalectomy
   b. Pituitary – transphenoidal resection, pituitary irradiation
   c. Ectopic production – antineoplastic therapy usually needed

Hirsutism

Hirsutism is defined as excessive hair growth in androgen-dependent areas in women – about 9% of young women report hirsutism and 4% seek advice (only 1-2% prevalence by objective scoring). Note that this is not necessarily pathological – in most cases it is a result from a combination of mildly increased androgen production and increased skin sensitivity to androgens (idiopathic hirsutism).

1. Classification:
   a. Androgen-dependent – beard, upper lip, chest, linea alba, upper back
      i. Due to increased production of androgens by the adrenal gland, ovary or both
      ii. May be coupled with increased skin sensitivity to androgens
      iii. Local conversion of testosterone to dehydrotestosterone by 5α-reductase
   b. Androgen-independent – trunk, cheeks
      i. May be inherited

2. Aetiology
   a. 95% have PCOS → oligomenorrhoea, insulin resistance, obesity, acne
   b. <1% have androgen-secreting tumour (adrenal/ovary)
   c. <1% have adrenal enzyme defects (e.g. 21-hydroxylase deficiency)
   d. <1% have acromegaly

3. Evaluation:
   a. Exclude tumours, Cushing, acromegaly via history and exam
   b. Serum testosterone (normal <6mmol/L), DHEA, 17-OH-progesterone (CAH)
   c. Radiology – ovarian ultrasound (20% have features), MRI ovaries/adrenals (rarely done)

4. Treatment – may need 6-9 months for improvement
   a. Mechanical – plucking, shaving, waxing, electrolysis etc.
   b. OCP – increases hormone binding globulin, decreases free androgens, suppresses LH
   c. Anti-androgens (spironolactone, cyproterone acetate, flutamide) block action at the receptor
   d. 5α-reductase inhibitors (Finasteride) – not funded
   e. Metformin improves virilisation, hirsutism and weight (useful for PCOS)

Parathyroid Disorders and Calcium Metabolism

1. General Principles

Calcium regulation is essential for many intracellular processes. Normal intake is 0.5-1.0g/day, of which 20-40% is absorbed – if intake or absorption is reduced, or requirements increase, a negative calcium balance may occur which can lead to a significant compensatory loss of calcium from bone

a. Parathyroid hormone is secreted by the chief cells of the parathyroid gland in response to hypocalcaemia; it is the principle regulator of extracellular calcium concentration by
   a. Stimulating calcium release from bone by increasing osteoclast bone resorption
2. Vitamin D is a steroid hormone that is ingested in the diet or produced from 7-dehydrocholesterol in the skin after exposure to ultraviolet light.
   a. The active form is produced by hydroxylations in the liver and kidney by 25-hydroxylase and 1-α-hydroxylase, which is stimulated by PTH, low ambient inorganic phosphate, growth hormone, prolactin and oestrogen. Note most circulating vitamin D is 25-OHD (calcidiol).
   b. 1,25-dihydroxy-vitamin D acts by increasing the efficiency of calcium absorption from the proximal small intestine and stimulating calcium release from bone; it also promotes phosphate absorption of the gut (in deficiency, renal excretion increases due to high PTH)

3. Other hormones that are involved in calcium homeostasis include calcitonin (inhibit osteoclast bone resorption), steroid hormones and local hormones (mediate skeletal actions of systemic hormones)

## Osteoporosis

Osteoporosis is defined functionally as low bone mass and subsequent increased fracture risk. It is defined clinically as symptomatric osteopenia (fractures) or bone mineral density >2.5 standard deviations below the mean, with normal values based on nomograms with age and gender correlations.

1. **Pathophysiology:**
   a. Normal bone turnover is a lifelong continuous process, each cycle taking about 8 months
      i. Osteoclasts on the surface of bone resorb old bone
      ii. Osteoblasts appear at resorption sites and fill the site with new osteoid
      iii. Osteoid becomes mineralised
   b. Increased osteoclast activity in a major contributor in newly post-menopausal women. This is a rapid process just after menopause begins, and continues for up to 3 years.
   c. Osteoblast activity also increases at this stage, but to a lesser degree – in fact, osteoblast numbers and activity tends to decrease in both sexes with age contributing to the imbalance
   d. In osteoporosis osteoclastic activity continues – while the amount of bone loss is minimal, there is significant loss of structural and trabecular integrity

2. **Clinical features:**
   a. Fractures are the main symptom – vertebrae (32%), hip (20%), forearm (19%), lower leg (19%), ribs (12%), humerus (11%)
      i. Lifetime risk for fractures – 1 in 2 females, 1 in 3 males
      ii. Risk factors – family history, age, smoking, prior fracture, bone density and low BMI
   b. Assessment by bone densitometry (DEXA scan), fracture history (strongly predictive of future fractures) and clinical risk factors.
      i. DEXA should be performed at both vertebrae and femoral neck areas (best predictor for hip fracture risk); screening recommended for women with risk factors
      ii. T-score – number of standard deviations from average values in a young population
         1. Normal bone mass >-1
         2. Low bone mass -1 to -2.5
         3. Osteoporosis <-2.5

3. **Management:**
   a. Conservative – exercise (helps preserve bone density and improves muscle mass, strength and balance), fall reduction strategies
   b. Medical:
      i. Calcium – bone loss reduced by ~1/3 (normally 1%/yr), not used in renal lithiasis
      ii. Vitamin D – 30 minutes outside a day can halve the number of fractures
      iii. HRT – fantastic for bones (stokes loss of bone density, increases bone density and reduces fracture rate) but higher breast cancer risk, MI, stroke, thromboembolism
      iv. Bisphosphonates – bind to osteoclasts and/or bone sites to prevent resorption, note alendronate causes oesophagitis, so is given with a large glass of water sitting up
   c. New Zealand guidelines:
      i. T score >-1 → calcium
      ii. T score -2 to -3 → calcium + etidronate
      iii. T score <-3 → calcium + alendronate
      iv. All patients should receive vitamin D if 1,25-(OH)₂D is <50nmol/L

## Osteomalacia

Osteomalacia is a generalised skeletal disorder characterised by the accumulation of osteoid matrix which fails to mineralise. There are a wide variety of causes, which fall into three broad categories:

1. Calcium deficiency is commonly associated with abnormalities of vitamin D metabolism:
   a. Inadequate exposure to ultraviolet light – elderly, institutionalised
Endocrinology

b. Inadequate dietary vitamin D – important when skin synthesis is reduced
c. Enhanced catabolism of 25-OHD in the liver and kidney, due to chronic calcium deprivation or enzyme induction (anticonvulsants) – this produces 2° hyperparathyroidism and ↑calcitriol
d. Abnormalities of the 1α-hydroxylase enzyme – inherited (vitamin D dependent rickets type 1) or acquired (chronic renal failure)
e. Failure of 1,25-(OH)2D to act 2° to receptor abnormality (vitamin D dependent rickets type 2)

2. Phosphate deficiency – commonly associated with impaired renal tubular phosphate reabsorption
   a. Usually congenital and involving phosphate transport alone (vitamin D resistant rickets) or with multiple renal tubular defects (Fanconi syndrome)
   b. Can also be acquired (tumour osteomalacia)

3. Osteoblast failure
   a. Abnormal osteoblast function may be congenital (hypophosphatasia) or acquired (etidronate, aluminium toxicity)
   b. Aluminium toxicity is most commonly seen in dialysis patients (exposure to dialysate, phosphate binding drugs and ability to excrete)

Clinical aspects:

1. Clinical features vary according to age
   a. In children osteomalacia causes rickets (deformity, growth retardation, swollen epiphiyses)
   b. In adults bone pain is the main feature, though there is also increased fracture risk

2. Biochemistry:
   a. Calcium deficiency – ↓Ca2+, ↓N PO4-3, ↑↑ALP, ↓25-OHD, ↑PTH
   b. Phosphate deficiency – ↓Ca2+, ↓↓PO4-3, ↑↑ALP, ↓N 25-OHD, N PTH
   c. Osteoblast failure – N↑Ca2+, N PO4-3, N↓ALP, N 25-OHD, N↓PTH

3. Radiology:
   a. Children – rickets is easily recognisable with epiphyseal abnormalities
   b. Adults – osteomalacic bones may just look osteopenic, may have Looser’s zones (pseudo-fractures; rare but diagnostic)

4. Treatment:
   a. Calcium deficiency – supplemental Ca2+ with either vitamin D (if 25-OHD is low) or with 1α-hydroxylated derivatives (if the problem is defective 1,25-(OH)2D production)
   b. Phosphate deficiency – supplemental PO4-3 with 1α-hydroxylated vitamin D derivatives, surgery if tumour rickets is present
   c. Osteoblast failure – withdraw etidronate, deplete aluminium from bone with desferroxamine

• Paget Disease

Paget disease is a focal disorder characterised by greatly increased rates of bone resorption and formation in affected bones. It is largely a disease of older Europeans, with the highest incidence in the northwest of England (up to 6% of Europeans over 55 have the disease). It is common in Europe (except Scandinavia), USA, Australia and New Zealand.

1. Aetiology is unknown, but there appear to be both genetic factors (40% have family history) and environmental factors including possible viral triggers (canine distemper and the measles virus)

2. Pathophysiology – arises in one ore more bones simultaneously, spreads within bones but not between; occasionally (<1%) transforms to osteosarcoma
   a. Initial ‘hot’ phase – intense osteoclastic activity leading to bone resorption
   b. Mixed (osteoclastic-osteoblastic) phase – reactive osteoblasts try to keep up with osteoclast mediated lysis; pagetoid bone (highly vascular) is laid down while destruction continues
   c. Final ‘cold’ phase – osteolysis slows, new bone synthesis by osteoblasts continues but is sclerotic (hard and dense, highly vascular) and cannot be remodelled → more brittle

3. Clinical features – common asymptomatic and detected as an incidental finding
   a. Bone pain is characteristic, there may also be deformity (long bones), microfractures, cranial nerve problems, 2° osteoarthritis, loose teeth (jaw involvement), heart failure and ↑Ca2+
   b. Radiology – raised bone density, coarse trabeculae (linear pattern), thickened cortex, loss of cortical-medullary junction, may have mixed sclerotic and lytic lesions (‘flamed shape’)
   c. Investigations – increased bone turnover markers (ALP; urinary pyridinoline, hydroxyproline and NTx); serum PTH, calcium and phosphorus levels monitored; histology characteristic

4. Treatment:
   a. Antioestoeclastic drugs reduce bone resorption and produce a 2° decrease in bone formation – they are effective in relieving pain, reducing bone turnover and healing lytic lesions
      i. Options include calcitonins (largely obsolete) and bisphosphonates (etidronate, clodronate, pamidronate, alendronate, risedronate, tiludronate and ibandronate)
      ii. All work effectively, provided sufficient dose is delivered – note that the dose of etidronate that can be given is limited by the occurrence of mineralisation defects
Endocrinology

b. Treatment is not curative, but remission of variable duration can be achieved before the disease relapses. Repeat courses can be given.

c. Surgery is required for fractures and joint replacement following 2° osteoarthritis

<table>
<thead>
<tr>
<th>Bone Resorption</th>
<th>Bone Formation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>↑ osteoclast numbers</td>
<td>↑ osteoblast numbers</td>
</tr>
<tr>
<td>Giant osteoclasts</td>
<td>Woven bone</td>
</tr>
<tr>
<td>Marrow fibrosis</td>
<td>Woven osteoid</td>
</tr>
<tr>
<td>Biochemistry</td>
<td></td>
</tr>
<tr>
<td>↑ hydroxyproline excretion</td>
<td>↑ alkaline phosphatase</td>
</tr>
<tr>
<td>Radiology</td>
<td></td>
</tr>
<tr>
<td>Lysis</td>
<td>Sclerosis</td>
</tr>
</tbody>
</table>

PAEDIATRIC ENDOCRINOLOGY

• Delayed Puberty and Calcium Disorders

Delayed puberty is defined as lack of secondary sexual characteristics in both genders by age 13. It is associated in both genders with short stature (50%). Investigations should include FBC and ESR, TFTs, GH provocation testing (2 stimuli), LH and FSH, GnRH stimulation test, bone age, and karyotype.

1. Constitutional delay of growth and development is generally a diagnosis of exclusion.
   a. Family history, normal birth weight, short stature from infancy with normal height velocity during childhood; delayed dentition and delayed bone age (>1 year)
   b. Delayed puberty with prepubertal growth slump but catch-up growth with onset of puberty

2. Turner syndrome – due to XO, XX XO mosaicism (>50%) or specific genes on the X chromosome
   a. Often low birth weight, short stature evidence by early childhood (commonest presentation), height velocity usually 4-5 cm/year (<3rd percentile)
   b. Approximately 30-50% only exhibit short stature and pubertal failure; though >90% have primary hypogonadism due to premature ovarian failure

3. Primary hypothyroidism – usually Hashimoto thyroiditis, rarely mild congenital hypothyroidism
   a. Often present for years before presentation with dramatic growth failure
   b. Infantile body proportions and very delayed bone age (indicator of duration)

4. Occult disease – always take a thorough systems enquiry
   a. Anorexia nervosa
   b. Renal disease – renal failure secondary to reflux nephropathy
   c. Gastrointestinal disease – coeliac disease, inflammatory bowel disease

5. Hypopituitarism – isolated GH deficiency or with gonadotropin deficiency, most commonly due to idiopathic, craniopharyngioma and germinoma.

Calcium disorders

1. Nutritional rickets is usually due to vitamin D deficiency, occasionally calcium deficiency. It is common in dark skinned ethnicities (Indian, Asian, middle-Eastern) and typically a combination of poor sunlight exposure and limited range of vitamin D containing dairy products.
   a. Clinical features – weakness, hypotonia, delayed gross motor milestones, irritability
      i. Signs – hot, swollen wrists, open fontanelles, craniotabes (thinning of cranial bones), rickety rosary (swelling of costochondral junctions), long bone bowing
      ii. Investigations – 25-OHD low, 1,25-(OH)2D normal (PTH action on 1-α-hydroxylase), high PTH (inadequate Ca+2 absorption), high ALP (bone turnover), ↓Ca+2, ↓PO4-3
      iii. Radiology – poorly developed epiphyses, widened growth plates, frayed and cupped metaphyses, cortical thinning, osteopenia, long bone bowing
   b. Treatment
      i. Address lifestyle and diet (may also have associated iron deficiency)
      ii. Massive dose of vitamin D (Stoss therapy, avoids significant hypercalcaemia) or active vitamin D (1-α-OHD) or calcitriol (1,25-(OH)2D) daily for three months
   c. Prognosis:
      i. May take 6-8 weeks to see radiological evidence of healing and normal ALP
      ii. Deformities in children <4 years of age usually completely correct

2. X-linked hypophosphataemic rickets is usually familial, with males more severely affected (often short stature and bowed legs in adult relatives); suspect in recurrent ‘nutritional’ rickets
   a. Usually presents in the first 2 years of life with striking lower limb bowing, short stature, dolichocephaly (helmet-shaped head); no weakness, hypotonia or irritability
   b. Investigations – serum PO4-3 low (defective tubular resorption) with inappropriately low or normal 1,25-(OH)2D (should be high 2° to low PO4-3), moderately raised ALP
   c. Treatment involves phosphate and vitamin D therapy throughout childhood to reduce bowing and bone pain, and to promote more normal growth
Thyroid disorders in infancy can be divided into congenital and transient hypothyroidism:

1. Congenital hypothyroidism has an incidence of 1 per 4,360 in New Zealand.
   a. 40% have athyroidism
   b. 40% have ectopia (usually sublingual remnant)
   c. 15% have dyshormonogenesis (usually organification defect)
   d. 5% have transient hypothyroidism

2. Transient hypothyroidism is due to excessive iodine exposure, maternal goitrogens, transplacentally derived TSH-receptor blocking antibodies, or endemic iodine deficiency
   a. Excessive iodine blocks iodine oxidation (Wolff-Chaikoff effect) – this is exaggerated in neonates, particularly premature. Sources include cord-cleaning solution, surgical sterilising solutions, and maternal iodine (e.g. asthma drugs)
   b. Endemic iodine deficiency leads to endemic goitre and maternal iodine deficiency – very common in underdeveloped countries but rare in NZ after the introduction of iodized salt

3. Thyroid hormone actions – note cretinism (spastic diplegia, mental retardation, squint, poor hearing)
   a. Brain development from the first trimester to the second year of life
   b. Development of the organ of Corti (hearing impairment)
   c. Normal growth (profound growth failure, infantile proportions, delayed bone age)
   d. Normal metabolism

Assessment and management:

1. Investigations need to be done urgently (within 24 hours of high TSH notification) – TSH, free T4, free T3, consider thyroid scintiscan (before T4 given, detects athyroidism/ectopia), bone age (knees)
2. Treatment – T4 therapy before 2nd week (binds to brain before being deiodinated to T3), dose 10-15μg/kg/day. Monitor T4 and TSH frequently until 2 years; aim for T4 in upper half of normal range
3. Prognosis – normal development despite athyroidism as T4 crosses placenta (except if deficiency endemic); if T4 is normalised before the 3rd week and maintained, intellectual function is normal.

Maternal thyrotoxicosis carries a risk of neonatal thyrotoxicosis (<2%), determined by the titre and affinity of maternal TSH receptor stimulating antibodies. Note if the first infant is affected, all subsequent children will be affected. These children have learning difficulties and low IQ, possibly due to accelerated myelinosis.

1. Carbmazole passes through the placenta so the neonate is at risk of transient thyroid suppression in the first few days – note propylthiouracil doesn’t cross the placenta but needs more frequent dosing
2. Maternal IgG also crosses the placenta, causing hyperthyroidism after a few days and lasting 4-6 weeks – if untreated this has a 20% mortality due to heart failure and arrhythmias
3. Treatment is with Lugol’s iodine immediately (utilises Wolff-Chaikoff effect) until euthyroid, then give carbimazole. Propanolol is used short-term to block sympathomimetic effects until euthyroid

TUTORIALS

• DKA, IV Insulin and Hypoglycaemia

Case One – Diabetic Ketoacidosis

A 17-year-old European male presents with a 2-week history of exhaustion, weight loss (6kg), excessive thirst, polyuria and nocturia. Over the 24 hours prior to admission he has become increasingly drowsy and on the morning of his admission his parents had difficulty waking him from sleep. Vomitus was on the pillow.

On examination: BP 65/40, HR 100, JVP very low, skin turgor reduced, Kussmaul respiration

Labs: Na+ 142, K+ 6.1↑, creatinine 0.21↑, HCO3 3↓↓, pH 6.91↓↓↓, glucose 36.2↑↑↑, urine ketones +++

1. What is your management with regards to fluids, electrolytes and insulin?

   a. Fluids urgently – severely hydrated (up to 100mL/kg) ⇒ aim for euvolaemia by 24-48 hours
      i. Normal saline 1L stat over the first hour
      ii. 0.5-1L of NaCl 0.9% (0.45% if Na+ >146mmol/L) over next 2 hours
      iii. Monitor U&Es – replace K+ at 20mmol/L when K+ <5.0 and urine output >30mL/hr

   b. Insulin should be taken slowly as glucose will often fall significantly with rehydration alone
      i. Give a stat dose iv of 10U of Actrapid or Humulin R, then continue by protocol
      ii. Once glucose is <15mmol/L introduce 5% dextrose at 1.5-2.0mL/kg/hr to switch off ketosis, replete glycogen and replace free H2O deficit
Endocrinology

2. Should the patient have the following?
   a. Nasogastric tube – if still experiencing nausea and vomiting (decompress stomach)
   b. Urinary catheter – useful to monitor urine output, but may be able to cope without
   c. CVL – if peripheral venous access can’t be gained (alternative is a venous cut-down)

3. What clinical and laboratory parameters should be monitored?
   a. Observations – level of consciousness, HR, RR, BP, hydration/fluid balance
   b. K+ and other electrolytes, glucose, urea, creatinine (hourly, then 2 hourly, then 6 hourly)

4. When can he be changed to subcutaneous insulin?
   a. Must have received 24 hours of fluids, patient is eating and urinary ketones are gone
   b. Rule of thumb – 0.2-0.3U/kg/day for Type 1, 0.4-0.5U/kg/day for Type 2

Case Two – Hyperglycaemic Hyperosmolar Non-Ketotic Syndrome
A 72-year-old man presents with a 2-week history of excessive thirst, polyuria and nocturia. He has been
told by his GP that he had ‘borderline diabetes’ some five years earlier. He has been quenching his intense
thirst with Coca-Cola, recently about 3L per day. On the evening prior to admission he felt very sleepy and
went to bed early. The next morning his wife found him difficult to wake and somewhat incoherent.
On examination: BP 110/60, HR 95, JVP very low, skin turgor reduced, tongue dry
Labs: Na+ 165 ↑↑↑, K+ 5.7 ↑, creatinine 0.23 ↑, HCO3=19, pH 7.38, glucose 72.5 ↑↑↑, urinary ketones +

1. How much glucose is in Coca-Cola?
   a. 11.5g per 100mL

2. How does management differ from DKA?
   a. Fluids – debatable. Starting off with 0.45% saline is logical, but there is risk of worsening
      oedema due to rapid fluid shifts; ADHB protocol is as for above (adjust for clinical/labs)
   b. Insulin – as above, may need a higher dose as the patient is quite possibly insulin resistant
   c. Others – aspirin, heparin or LMWH for thromboembolism prophylaxis

3. If he has type 2 diabetes, when and how would you take him off insulin?
   a. Take him off insulin and fluids when glucose stable at 10-12mmol/L and he is eating/drinking
   b. Check HbA1c – if <10, think about metformin (unless GFR <15mL/min) or a sulfonyurea

Case Three - Hypoglycaemia
A 25-year-old woman with type 1 diabetes of 19 years duration is admitted to hospital following a MVA. She
is unconscious but has no obvious injuries and no focal neurological signs. Her blood sugar is 0.9mmol/L.

1. What are the important counter-regulatory hormones to hypoglycaemia?
   a. Glucose, cortisol, adrenaline and growth hormone
   b. Note long-standing type 1 diabetes can lead to α cell atrophy

2. Describe immediate management.
   a. Take fingerprick blood glucose and/or laboratory blood glucose
   b. 100mL of glucose 10% iv (or 50mL 50% dextrose)
   c. When she has regained consciousness, give her food (complex carbohydrate)

3. When she recovers, what information would you need to explain this episode and prevent
   more? What is hypoglycaemic unawareness?
   a. Precipitating causes – alcohol, dose of insulin/sulfonylurea too high, starvation
   b. Hypoglycaemic unawareness – repeated episodes leads to loss of physiological response

4. What advice would you give regarding management of hypoglycaemia in the future?
   a. Mild – oral glucose/sucrose, meal (complex carbohydrates)
   b. Severe – glucagon IM, hypostop gel, consider calling ambulance

Case Four – Hypoglycaemia
A 72-year-old woman with type 2 diabetes of 12 years duration is admitted with collapse. She is taking
glibenclamide 10mg bd. Investigations show blood glucose of 1.3mmol/L and plasma creatinine 0.19.

1. Describe immediate management:
   a. Take fingerprick blood glucose and/or laboratory blood glucose
   b. 100mL of glucose 10% iv (or 50mL 50% dextrose)
   c. 10% glucose 100mL per hour for at least 48 hours
   d. Others – stop glibenclamide, consider subcutaneous octreotide (somatostatin analogue)

2. What factors have contributed?
   a. Long half-life of glibenclamide (T1/2 12-24 hours)
   b. Glibenclamide is renally excreted - ? renal impairment

3. What changes would you make to her treatment?
   a. Consider metformin or gliclazide – T1/2 is 6-8 hours, and metabolism is 50% hepatic
Endocrinology

- Insulin Types, Analogues, Schedules, Dose Adjusting and How to Start Insulin

Injecting:
1. 3 types of syringes (100U/1mL, 50U/0.5mL and 30U/0.3mL), generally 1000U per 10mL bottle
   a. Draw up air to amount required, inject into ampoule
   b. Draw up to the top of the black stopper
2. Injection sites should be varied to avoid fat hypertrophy
   a. Belly best – into fat, not muscle
   b. Thigh is good for depot
3. Pen devices are nifty – 32G needle (change when blunt), one click is one unit
   a. Need to shake to resuspend ampoule (doesn’t need refrigeration once in the pen)
   b. Note you need one pen per type of insulin ± a backup

Types of insulin:

<table>
<thead>
<tr>
<th>Activity</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fast acting</td>
<td></td>
</tr>
<tr>
<td>Novo  Novorapid</td>
<td>Good for dinner</td>
</tr>
<tr>
<td>Lilly Humalog (Lispro)</td>
<td></td>
</tr>
<tr>
<td>Activity</td>
<td></td>
</tr>
<tr>
<td>Novo  Novorapid</td>
<td>Good for dinner</td>
</tr>
<tr>
<td>Lilly Humalog (Lispro)</td>
<td></td>
</tr>
</tbody>
</table>

Schedules – once daily (good for starting in type 2 patients), twice daily (breakfast and dinner), basal/bolus (almost exclusively type 1 diabetes as type 2 patients don’t need basal insulin), insulin pumps ($6,000, but lifestyle benefits – risk of DKA)

Case study:
A 65-year-old man with known type 2 diabetes for 15 years consults you about his metabolic control. Despite keeping as much as possible to a sensible diet and walking twice weekly, his HbA1c remains at 8.9%. Home glucose recordings are often in double figures, and he generally feels a bit tired. Current medication is Metformin 850mg bd and Gliclazide 160mg bd. He can’t afford thiazolidinediones.

1. What is the mechanism of action of thiazolidinediones and acarbose?
   a. Thiazolidinediones – PPAR-γ receptor activators, extremely potent insulin sensitiser
   b. Acarbose – ‘Xenical for diabetes’; inhibits α-glucosidase (complex carbohydrate breakdown)
2. How do you start him on insulin?
   a. Protophane at night – liver produces glucose at night, can wake with even higher glucose
   b. Give 0.1-0.2U/kg, then increase every 5 days by 5U until ~50U (consider altering schedule if still problematic e.g. Penmix 30/70; 2/3 mane and 1/3 nocte)
   c. Continue metformin where possible, as this decreases requirements by about a third
3. What problems may he encounter with insulin use?
   a. Hypoglycaemia
   b. Weight gain – anabolic, poor metabolic control (renal threshold ~10mmol/L glucose)