

Third edition

Notes & Notes

For MRCP part 1 & 11

By

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Endocrinology

&

Metabolism

Updated 2022

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The 10 Golden Tips for MRCP written exams you will ever need

1. For MRCP, do not read hard; read smart.
2. Three to six months is usually enough for preparation.
3. Practice the best of the five questions as much as possible.
4. The few days before the exam date, stop revising questions and concentrate on your MRCP notes and top tips.
5. Remember, you are getting ideas and concepts from the questions.
6. Time factor in the exam room is the leading killer after poor preparation.
7. Manage your time wisely.
8. Read the end of the question first; if you can answer it without reading the whole scenario, it will save your time for the other tuff question (long scenario, .what is the action of imatinib?)
9. Take care for any single word in the question, e.g. (the initial test, the diagnostic test, the best test, the next step)
10. Practice, practice and practice.



Contents

Chapter 1 Endocrinology & Metabolism

Antidiuretic hormone (ADH) (Vasopressin)	2	Familial hypocalciuric hypercalcaemia (FHH)	70
Syndrome of inappropriate ADH secretion (SIADH) (\uparrow ADH)	3	Hypocalcaemia	70
Diabetes insipidus (DI)	4	Magnesium (Mg)	73
Water deprivation test	5	Hypomagnesaemia	74
Polyuria - Hyponatraemia	9	Hypermagnesaemia	76
Hypopituitarism	11	Vitamin D (calciferol)	77
Growth hormone (GH)	14	Vitamin D deficiency	78
Growth hormone deficiency (GHD)	16	Phosphate.....	80
Acromegaly	18	Hypophosphataemia.....	81
Laron's syndrome	19	Hyperparathyroidism.....	83
Nelson syndrome (post adrenalectomy syndrome)	22	Primary hyperparathyroidism.....	84
Pituitary adenoma	22	Secondary hyperparathyroidism.....	87
Pituitary apoplexy	23	Tertiary hyperparathyroidism.....	88
Hyperprolactinaemia	25	Hypoparathyroidism	88
Physiological effects of thyroid hormones	26	Pseudohypoparathyroidism.....	89
Calcitonin	30	Pseudo pseudohypoparathyroidism.....	90
Hypothyroidism	32	Osteomalacia.....	90
Pendred's syndrome - Riedel's thyroiditis	33	Osteopetrosis - Osteoporosis.....	92
Sick euthyroid syndrome - Subclinical hypothyroidism	37	Glucocorticoid-induced osteoporosis.....	94
Abnormal thyroid function - Post-partum thyroiditis	38	Osteoporosis: assessing fracture risk.....	95
Subacute (De Quervain's) thyroiditis	40	Osteoporosis: management.....	97
Subclinical hyperthyroidism	41	Adrenal gland: Basics.....	101
Thyrotoxicosis	42	Premature adrenarche.....	101
Toxic multinodular goitre (TNG) (Plummet's disease)	43	Dehydroepiandrosterone sulphates (DHEAS)	102
Toxic thyroid adenoma (solitary toxic nodule)	48	Cortisol.....	103
Graves' disease	49	Aldosterone.....	104
Antithyroid drugs	50	Adrenal hyperandrogenism.....	105
Radioactive iodine therapy (RAI)	52	Hyperaldosteronism: Overview.....	106
Thyroidectomy	53	Primary hyperaldosteronism.....	107
Amiodarone and the thyroid gland	54	Aldosterone receptor antagonists.....	110
Thyroid eye disease	55	Adrenal incidentaloma.....	111
Thyroid storm (crisis)	57	Congenital adrenal hyperplasia (CAH)	112
Thyroid cancer	59	Glucocorticoid remediable aldosteronism (GRA)	117
Thyroid nodule and fine-needle aspiration	60	Pseudohyperaldosteronism.....	119
Calcium metabolism	64	Syndrome of Apparent Mineralocorticoid Excess (SAME)	119
Hypercalcaemia	66	Phaeochromocytoma.....	120
	67	Primary hypoadrenalinism (Addison's disease).....	123

Chapter 1 Endocrinology & Metabolism

Addisonian crisis.....	128	Diabetes mellitus: DVLA.....	196
Secondary hypoadrenalism.....	129	Insulinoma.....	198
Corticosteroids.....	131	Glucagonoma.....	200
Cushing's syndrome (Hypercortisolism)	133	Monogenic diabetes: Maturity-onset	
Pancreatic Hormones - Glucose transporters	140	diabetes of the young (MODY).....	201
Glycaemic index (GI).....	142	Latent autoimmune diabetes of adulthood (LADA)	202
Metabolic syndrome.....	143	Mitochondrial diabetes.....	203
Pre-diabetes or impaired glucose regulation (IGR).....	144	Diabetes in pregnancy.....	203
Diabetes mellitus: Type 1 overview.....	146	Gestational diabetes mellitus (GDM).....	204
Diabetes mellitus: management of type 1.....	148	Pre-existing diabetes in pregnancy.....	205
Diabetes mellitus: Type 2 overview.....	149	Obesity: overview.....	206
Glycosylated haemoglobin (HbA1c).....	151	Obesity: management (step-wise approach)	207
Diabetes mellitus: management of type 2	153	Lipid disorders: Overview.....	208
Biguanides (metformin).....	157	Familial Combined Hyperlipidaemia (type IIB)	210
Sulphonylureas.....	158	Remnant hyperlipidaemia (type III).....	211
Meglitinides.....	160	Familial hypertriglyceridaemia.....	211
Thiazolidinediones (glitazones, insulin sensitizers)	160	Familial hypercholesterolaemia (FH).....	213
Insulin: Basics.....	162	Secondary hypertriglyceridaemia.....	214
Insulin therapy.....	163	Hyperlipidaemia: management.....	217
Glucagon-like peptide-1 (GLP-1).....	165	Lipid-lowering agents.....	218
Glucagon-like peptide-1 (GLP-1) analogs	166	Statins.....	219
Dipeptidyl peptidase-4 (DPP-4) inhibitors (gliptins)	168	Fibrates.....	220
Sodium-glucose cotransporter 2 inhibitors (gliflozins)	169	Ezetimibe.....	221
Alpha-glucosidase inhibitors.....	170	Nicotinic acid (niacin)	221
Diabetic ketoacidosis (DKA): Overview	170	Cholestyramine.....	222
Diabetic ketoacidosis (DKA): Management	172	Tangier disease.....	222
Hypoglycaemia.....	177	Abetalipoproteinemia.....	223
Diabetes mellitus: early morning hyperglycemia	180	Gynaecomastia.....	224
Hypoglycaemia unawareness (HU).....	180	Physiological changes during pregnancy – endocrine	224
Hyperosmolar hyperglycaemic state (HHS)	182	Physiological effects of LH, FSH, and sex hormones	225
Diabetes mellitus: hypertension management	183	Dihydrotestosterone (DHT).....	226
Post prandial pain in diabetics.....	184	Polycystic ovarian syndrome (PCOS)	228
Diabetic retinopathy.....	184	Hirsutism.....	230
Diabetic neuropathy.....	188	Hypertrichosis.....	231
Diabetic autonomic neuropathy.....	191	Amenorrhoea.....	231
Diabetic amyotrophy.....	191	Premature ovarian failure.....	232
Diabetic foot.....	193	Menopause.....	233
Diabetic neuropathic arthropathy (Charcot foot)	194	Hormone replacement therapy (HRT).....	234
Necrobiosis lipoidica diabetorum.....	195	Selective Estrogen Receptor Modulators (SERMs)	235

Chapter 1 Endocrinology & Metabolism

Androgen insensitivity syndrome.....	236	Delayed puberty.....	240
Disorders of sex hormones.....	237	Multiple endocrine neoplasia.....	242
Menstrual cycle.....	237	Autoimmune polyendocrinopathy syndrome (APS) (Polyglandular syndrome).....	245
Hypogonadism.....	238		

Chapter 2 Pulmonology

Lung anatomy.....	248	Pseudomonas pneumonia.....	304
Diaphragmatic paralysis (Phrenic nerve palsy)	250	Hospital-acquired pneumonia (HAP).....	305
Lung physiology.....	250	Pneumocystis Jirovecii pneumonia (PCP).....	306
Oxygen Dissociation Curve.....	252	Coronavirus disease 2019 (COVID-19).....	308
Pulmonary function tests.....	255	Aspergillosis: Types.....	311
Obstructive vs. Restrictive lung diseases	255	Allergic bronchopulmonary aspergillosis (ABPA).....	312
Transfer factor.....	258	Aspergilloma.....	313
Transfer coefficient of carbon monoxide (KCO)	259	Invasive aspergillosis (IA).....	314
Arterial Blood Gas (ABG).....	260	Alpha-1 antitrypsin (A1AT) deficiency.....	316
Chest x-ray.....	262	Acute respiratory distress syndrome (ARDS).....	318
Pleural calcification - Solitary pulmonary nodules	265	Altitude related disorders.....	321
Alveolar-arterial (A-a) oxygen gradient.....	266	Bronchiectasis.....	322
Finger clubbing.....	267	Cystic fibrosis (CF).....	325
Respiratory failure.....	268	Occupational asthma.....	331
Bronchial Asthma.....	269	Hypersensitivity pneumonitis (HP).....	332
Acute severe asthma.....	274	Pneumoconiosis.....	334
Chronic Obstructive Pulmonary Disease(COPD)	276	Asbestos and the lung.....	335
COPD: stable management.....	279	Pleural mesothelioma.....	335
Non-invasive ventilation (NIV).....	283	Silicosis.....	337
Invasive ventilation.....	285	Berylliosis.....	339
Long-term oxygen therapy (LTOT).....	285	Coal workers' pneumoconiosis (CWP).....	340
Pulmonary embolism (PE).....	286	Primary ciliary dyskinesia (PCD).....	341
Recurrent pulmonary emboli.....	291	Kartagener's syndrome.....	342
Pulmonary embolism in pregnancy: diagnosis and management.....	291	Lung cancer: General overview.....	343
Fat embolism.....	293	Lung cancer: paraneoplastic features.....	346
Community-acquired pneumonia (CAP)	294	Lung cancer: stepwise investigations.....	347
Klebsiella Pneumonia.....	298	Performance status for patient of lung cancer and COPD	349
Legionella pneumonia (Legionnaires' disease)	299	Staging lung carcinoma.....	349
Mycoplasma pneumoniae.....	300	Treatment of lung cancer.....	351
Aspiration pneumonia.....	302	Lung cancer induced superior vena cava obstruction (SVCO).....	353
Psittacosis (Chlamydia psittaci pneumonia) (Atypical pneumonia).....	303	Pancoast tumor.....	354
		Lung metastases.....	355

Chapter 2 Pulmonology

Carcinoid lung tumour.....	356	Chronic eosinophilic pneumonia.....	374
Lung fibrosis: Causes.....	357	Tropical pulmonary eosinophilia.....	375
Idiopathic pulmonary fibrosis (IPF)	358	Loffler's syndrome.....	376
Bronchiolitis obliterans (BO).....	360	Cryptogenic organising pneumonia (COP)	376
Post-extubation stridor (PES).....	362	Pulmonary hypertension (PH).....	377
Obstructive sleep apnoea (OSA).....	362	Sarcoidosis.....	379
Obesity hypoventilation syndrome (OHS)	364	Lofgren's syndrome.....	384
Pneumothorax.....	364	Yellow nail syndrome.....	384
Pleural effusion.....	368	Hepatopulmonary syndrome (HPS).....	385
Chylothorax.....	372	Pulmonary alveolar microlithiasis (PAM)	386
Haemothorax.....	372	Pulmonary Alveolar Proteinosis (PAP)	387
Eosinophilic Pulmonary Diseases.....	373	Carbon monoxide poisoning.....	388
Acute eosinophilic pneumonia.....	374	Smoking cessation.....	390

Chapter 3 Gastroenterology

Achalasia.....	296	Menetrier's disease.....	329
Dysphagia.....	299	Dyspepsia.....	329
Oesophageal disorders.....	300	Malabsorption.....	331
Gastro-oesophageal reflux disease (GORD)	301	Jejunal villous atrophy.....	332
Barrett's oesophagus.....	304	Coeliac disease.....	332
Oesophagitis in immunosuppressive patients	306	Whipple's disease.....	335
Eosinophilic oesophagitis.....	307	Tropical Sprue.....	336
Oesophageal cancer.....	307	Irritable bowel syndrome (IBS).....	336
Pharyngeal pouch.....	310	Malnutrition.....	338
Acute upper gastrointestinal bleeding (UGIB)	311	Lactose intolerance.....	339
Oesophageal varices.....	314	Functional constipation.....	339
Esophageal Rupture.....	315	Energy from food.....	340
Hiccup.....	317	Protein losing enteropathy.....	340
Helicobacter pylori.....	317	Enteral feeding.....	341
Peptic ulcer.....	319	Refeeding syndrome.....	342
Zollinger-Ellison syndrome.....	321	Melanosis coli.....	343
Somatostatin.....	323	Mesenteric ischaemia (ischaemic colitis)	344
Somatostatinoma.....	323	Small bowel bacterial overgrowth syndrome (SBBOS)	345
Gastric MALT lymphoma.....	323	Spontaneous bacterial peritonitis (SBP)	346
Gastroparesis.....	324	Abdominal tuberculosis (Tubercular peritonitis)	347
Gastric cancer.....	325	VIPoma.....	347
Gastrointestinal stromal tumour (GIST)	328	Volvulus.....	348

Chapter 3 Gastroenterology

Imaging in bowel obstruction.....	349	Alcoholic ketoacidosis.....	388
Radiology: pneumoperitoneum.....	351	Non-alcoholic fatty liver disease (NAFLD).....	388
Dumping syndrome.....	352	(Non-alcoholic steatohepatitis (NASH).....	388
Small bowel lymphoma.....	352	Liver abscess.....	391
Acute pancreatitis.....	353	Hydatid cysts.....	392
Systemic inflammatory response syndrome (SIRS).....	357	Drug-induced liver disease.....	393
Pancreatic pseudocysts.....	357	Budd-Chiari syndrome.....	393
Chronic pancreatitis.....	358	Gilbert's syndrome.....	394
Pancreatic cancer.....	359	Crigler-Najjar syndrome.....	394
Ascending cholangitis.....	360	Dubin-Johnson syndrome.....	394
Gallstones (Cholelithiasis).....	360	Autoimmune hepatitis.....	395
Functional gall bladder pain.....	362	Ischaemic hepatitis.....	396
Choledochal cysts.....	363	Physiological liver changes during pregnancy.....	396
Sphincter of Oddi dysfunction.....	363	Gilbert's & Dubin-Johnson syndrome.....	396
Post-cholecystectomy syndrome.....	364	HELLP syndrome.....	396
Bile-acid malabsorption.....	364	Obstetric cholestasis.....	397
Primary biliary cirrhosis.....	365	Acute fatty liver of pregnancy (AFLP).....	397
Primary sclerosing cholangitis (PSC).....	366	Haemochromatosis.....	398
Cholangiocarcinoma.....	368	Hepatocellular carcinoma (HCC).....	401
Hepatomegaly.....	369	Carcinoid syndrome.....	402
Hepatosplenomegaly.....	369	hepatic metastases.....	403
Liver function test.....	369	Hepatitis A (HAV).....	403
Liver biopsy.....	372	Hepatitis B.....	404
Acute liver failure.....	372	Hepatitis B and pregnancy.....	413
Ascites.....	372	Hepatitis C.....	413
Liver cirrhosis.....	375	Hepatitis D.....	417
Liver transplant.....	378	Hepatitis E.....	417
Portal hypertension.....	379	Hepatitis histology.....	418
Hepatic encephalopathy.....	381	Colorectal cancer (CRC).....	418
Hepatorenal syndrome (HRS).....	382	Colorectal cancer: screening.....	421
Wilson's disease.....	383	Colorectal cancer: referral guidelines.....	421
Hyponatraemia in Patients with chronic liver disease	385	AJCCC (American Joint Committee)	
Alcohol.....	385	Staging of Colorectal Cancer.....	423
Alcohol induced hypoglycemia.....	385	Dysplastic colonic polyps.....	425
Alcohol - drinking problems: management	386	Peutz-Jeghers syndrome.....	426
Disulfiram.....	386	Capsule endoscopy.....	426
Alcoholic liver disease.....	386	Pseudomyxoma peritonei.....	426
The common abnormalities in chronic alcohol dependence	387	Villous adenoma.....	427

Chapter 3 Gastroenterology

Carcinoid tumours.....	427	Toxic megacolon (Toxic dilatation of the colon)	552
Diverticular disease.....	428	Radiation enteritis.....	553
Meckel's diverticulum.....	431	Gastroenteritis.....	554
Intussusception.....	432	Diarrhoea.....	554
Aorto-enteric fistulae (AEF).....	432	Biochemical abnormalities in persistent vomiting	556
Angiodysplasia.....	432	Giardiasis.....	556
Anal fissure.....	434	Clostridium perfringens.....	557
Anal fistula.....	434	Bacillus cereus.....	557
Crohn's disease.....	435	Shigella.....	557
Crohn's-like enterocolitis with mycophenolate mofetil	442	Yersinia enterocolitica.....	557
Ulcerative colitis.....	442	Gastrointestinal parasitic infections.....	558
Inactive (quiescent) colitis.....	444	Exotoxins and endotoxins.....	559
Ulcerative colitis: colorectal cancer.....	446	Pseudomembranous colitis (<i>Clostridium difficile</i>)	561
Inflammatory bowel disease: key differences	447	Gastroenteritis (GI).....	563
IBD: histology.....	448	Scombrotoxin food poisoning.....	564
Microscopic colitis (Collagenous colitis and Lymphocytic colitis).....	449	Perforated viscus.....	564
Collagenous colitis.....	551	Endoscopy in patients on antiplatelet or	
Lymphocytic colitis.....	551	anticoagulant therapy.....	566

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Endocrinology

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Metabolism

Updated 2022

Pituitary gland conditions

Antidiuretic hormone (ADH) (Vasopressin)

Overview

- **Synthesized** in the supraoptic nucleus of the hypothalamus.
- **Stored and secreted from the posterior pituitary** gland
- it contains arginine, so called **arginine vasopressin (AVP)**
- Vasoconstrictive effects at higher levels
- Increase of urea reabsorption in the collecting duct: increases the corticomedullary gradient and facilitates urine concentration
- ACTH release

Functions

- 1) **Antidiuresis:** **Act on V2 receptors** → ↑↑ transcription and **insertion of water (Aquaporin-2) channels** into the apical membrane of distal convoluted tubule and collecting duct epithelial cells → ↑ water permeability → ↑ water reabsorption (retain water in the body) → excretion of more concentrated urine, i.e., **antidiuresis**.
- 2) **Act on V1 receptors** → **Increase smooth muscle contraction (Vasoconstriction)**, uterine, GI and indirectly ↓coronary artery blood flow).
- 3) **Increase release of von Willebrand & factor VIII.**, (**Desmopressin** used for haemophilia A & Von Willebrand disease).
- 4) **Increase platelet aggregation**, (prothrombotic at high dose).

Vasopressin receptors

Receptor	Second messenger	Location	Action	Agonist
V1 or (V1a)	G protein-coupled, phosphatidyl inositol/ calcium	◆ vascular smooth muscle, ◆ platelet, ◆ hepatocytes, ◆ myometrium	◆ vasoconstriction, ◆ myocardial hypertrophy, ◆ platelet aggregation , ◆ glycogenolysis, ◆ uterine contraction	◆ Terlipressin → ↑ splanchnic VC → ↓ esophageal varices bleeding. ◆ Felypressin → prolong the action of local anesthesia (safer than epinephrine in cardiac patients)
V3 or (V1b)	G protein-coupled, phosphatidyl inositol/ calcium	anterior pituitary gland	releases ACTH, prolactin, endorphins	
V2	Adenylate cyclase/ cAMP	Renal basolateral membrane of collecting duct,	Anti-diuresis (Insertion of aquaporin-2 channels)	◆ Vasopressin (weak , short acting , given SC or IM) ◆ Desmopressin (more potent, long acting, given intra-nasally)
		Extra renal (vascular endothelium)	↑↑ release of von Willebrand & factor VIII.	Desmopressin (used for haemophilia A & Von Willebrand disease)

Factors increase secretion of vasopressin (stimulatory factors):

- **Increased osmolality of plasma (The main stimulus).**
- Reduced extracellular volume, hypovolaemia, blood loss, and hypotension (less sensitive stimulus).
- decreased thirst perception and reduced fluid intake.
- Advancing age
- Angiotensin II
- **Hypoglycemia**
- Increased pain
- Opiates
- Nicotine
- Antineoplastic drugs
- **Carbamazepine**

Factors decreases secretion of vasopressin (inhibitory factors):

- genetic conditions (Wolfram syndrome),
- tumours (Craniopharyngioma, **Germinoma**),
- inflammatory conditions (Sarcoidosis, Histiocytosis).
- Ethanol (alcohol) → ↓ calcium-dependent secretion of AVP
- Atrial natriuretic peptide, by inhibiting Angiotensin II-induced stimulation of AVP secretion
- Cortisol

MRCPI-part-1- January 2018: H/O RTA + rapid pulse and low BP + low Na.

- What is the most likely explanation for this patient's hyponatremia?
 - ⇒ **Physiologic ADH (vasopressin) secretion**
 - **Hyponatremia that develops after massive hemorrhage is likely dilutional.**
 - When baroreceptors detect decreases in effective arterial volume, such as after massive blood loss, they cause antidiuretic hormone (ADH) to be released from the pituitary gland to increase renal reabsorption of free water, diluting serum sodium levels and causing hyponatremia.
- What is the appropriate management of this patient?
 - ⇒ **normal saline.**
 - Management of **hypovolemic hyponatremia** includes volume repletion with normal saline.
 - Correction of hypovolemia removes the stimulus to release ADH, causing free water excretion by the kidneys, which leads to rapid correction of serum sodium levels.
 - volume repletion with normal saline must occur at a slow rate, because rapid correction of hyponatremia can cause central pontine myelinolysis.

May 2016 exam -part-1: Which adaptive mechanism that prevent dying from dehydration?

→ **Increase of aquaporin-2 in the collecting duct.**

- ADH (vasopressin) → ↑ aquaporin-2 expression → ↓ water excretion → protect against dehydration

MRCPUK-part-1-january-2018: You are reviewing a patient with a history of cranial diabetes insipidus. He is passing 4–6 litres of urine per day.

Expression of which channel is likely to be decreased most in the collecting duct?

→ **Aquaporin 2**

- It is found in the apical membranes of collecting duct principal cells.
- Aquaporin 2 gene expression is increased by vasopressin, which leads to increased re-absorption of free water. Expression is therefore downregulated in response to cranial diabetes insipidus.

Syndrome of inappropriate ADH secretion (SIADH) ($\uparrow \text{ADH}$)

Definition

- The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is a disorder of impaired water excretion caused by the inability to suppress the secretion of antidiuretic hormone (ADH) leading to euvoalaemic, hypotonic hyponatraemia.

Causes

Category	Examples
Malignancy	<ul style="list-style-type: none"> • Small cell lung cancer (The most common cause) • Less common head and neck cancer, olfactory neuroblastoma
Neurological	<ul style="list-style-type: none"> • Stroke, subarachnoid haemorrhage, subdural haemorrhage • Meningitis/encephalitis/abscess
Infections	<ul style="list-style-type: none"> • Pneumonia, tuberculosis, symptomatic HIV,
Drugs	<ul style="list-style-type: none"> • Sulfonylureas , Thiazides • SSRIs, tricyclics, mono-amine oxidase uptake inhibitors, phenothiazines • carbamazepine • vincristine , vinblastine • cyclophosphamide, chlorpropamide • omeprazole
Other causes	<ul style="list-style-type: none"> • Surgical procedures • porphyrias (SIADH is associated with acute intermittent porphyria)

Mechanisms

- $\uparrow \text{ADH} \rightarrow \uparrow \text{water retention} \rightarrow \text{Euvolemic hyponatraemia}$ (dilutional effects) \rightarrow low plasma osmolality + high urine osmolality with an elevated urine sodium (above 20 mmol/L)
- Osmotic fluid shifts \rightarrow Cerebral edema and \uparrow intracranial pressure

Features

- Symptoms of hyponatremia (usually asymptomatic until the sodium level falls below 120 mmol/l)
 - ⇒ **Mild:** anorexia, nausea, vomiting, headache, muscle cramps (**the earliest symptoms** of acute hyponatremia are **nausea and vomiting.**)
 - ⇒ **Moderate:** muscle weakness, lethargy, confusion
 - ⇒ **Severe:** seizures, altered consciousness
- Normotensive
- Symptoms of the underlying condition

Diagnostic criteria: SIADH can only be diagnosed when the following criteria are satisfied:

1. The patient is clinically **euvolaemic** (no clinical evidence of fluid overload (oedema) or dehydration)
2. \downarrow **Plasma sodium** ($<134 \text{ mmol/l}$) → **hypoosmolality** ($<280 \text{ mOsm/kg}$)
3. \uparrow **Urine sodium** ($>20 \text{ mmol/l}$) and osmolality ($>100 \text{ mOsm/kg}$) → concentrated urine
4. Normal **thyroid, adrenal, and renal** function.
 - ⇒ It is important to note that normal thyroid is referring to primary hypothyroidism. **Euthyroid sick syndrome does not preclude the diagnosis of SIADH.**

Diagnostic criteria

Diagnostic criteria for SIADH

	Clinical and/or laboratory findings
Hyponatremia	\downarrow Serum sodium $< 135 \text{ mEq/L}$
Hypoosmolality	\downarrow Serum osmolality $< 275 \text{ mOsm/kg}$
Concentrated urine	\uparrow Urine osmolality $> 100 \text{ mOsm/kg}$
Elevated urinary sodium	\uparrow Urine sodium concentration $> 20 \text{ mEq/l}$
Euvolemia	<ul style="list-style-type: none"> ▪ No signs of hypovolemia ▪ No signs of hypervolemia (e.g. oedema)
No alternative causes	<ul style="list-style-type: none"> ▪ Normal thyroid, adrenal, and renal function → Other causes of euvolemic hypotonic hyponatremia have been excluded (e.g., hypothyroidism, hypercortisolism, AKI) ▪ It is important to note that normal thyroid is referring to primary hypothyroidism. Euthyroid sick syndrome does not preclude the diagnosis of SIADH.

Differential diagnosis

- Cerebral salt wasting (CSW)
 - ⇒ **hypovolaemia**, hyponatraemia and **grossly elevated urine sodium (>100)** in patient with head injury.
 - ⇒ it **treated with replacing fluid and sodium losses**, whereas SIADH treated with fluid restriction

SIADH patients are usually euvolemic, normotensive, and have no edema. A hyponatremic patient with edema should raise suspicion of other conditions (e.g. congestive heart failure)

Management

Restriction of water intake is the **initial treatment of choice** for hyponatraemic patients with **SIADH** who are not at imminent risk of seizures or coma. This precipitates a gradual rise in serum sodium, not greater than the recommended maximum of 8–10 mmol/day.

- **Severe acute symptomatic hyponatraemia:** (who present with neurologic abnormalities, e.g. seizures or ↓ conscious level).
 - ⇒ hypertonic (3%) saline given via continuous infusion
 - Infusion of hypertonic (3%) saline is **reserved for patients with acute severe life-threatening hyponatraemia**, usually where **sodium is less than 120 mmol/L** and there are significant neurological features (i.e. seizures or GCS less than 11).
 - ⇒ correction must be done slowly to avoid precipitating central pontine myelinolysis
 - The sodium serum levels may increase by a maximum of 10 mmol/L within 24 hours or 0.5 mmol/L per hour.
- **Mild acute OR chronic hyponatraemia:** ($\text{Na}^+ \geq 120$ and NO neurological signs)
 - ⇒ 1st line → **fluid restriction (the initial treatment of choice)**
- Restriction of fluid to a **daily intake of less than 800 mL/day**.
- patients with subarachnoid hemorrhage are an exception since fluid restriction may promote cerebral vasospasm.
 - ⇒ 2nd line → **demeocycline**
- it is a semi-synthetic tetracycline antibiotic → **reduces the responsiveness of the collecting tubule cells to ADH (by inducing nephrogenic diabetes insipidus)**
 - ⇒ 3rd line → ADH (vasopressin) receptor antagonists have been developed (ie. tolvaptan)
- Side effects → hepatotoxicity, excessive thirst

SIADH initial treatment:

- If there is obvious precipitant (eg: drug) → stop the precipitant agent
- where there is no obvious precipitant → **fluid restriction → demeclocycline**

Diabetes insipidus (DI)

Diabetes insipidus is characterised by a high plasma osmolality and a low urine osmolality

Definition

- The passage of large volumes (>3 L/24 hr) of dilute urine (< 300 mOsm/kg) due to deficiency of or insensitivity to antidiuretic hormone (ADH).

Types and mechanisms of DI

1. **Cranial DI:** caused by a **deficiency** of antidiuretic hormone (ADH) (**the most common type**)
2. **Nephrogenic DI:** caused by **insensitivity** to ADH (**rare**)
3. **Primary polydipsia (dipsogenic DI):** caused by a primary defect in osmoregulation of thirst.
4. **Gestational DI:** caused by degradation of vasopressin by a placental vasopressinase.

Causes of cranial DI

- Primary
 - ⇒ Idiopathic (the most common primary cause)
 - ⇒ Hereditary (rare): **Wolfram's syndrome (DIDMOAD)** : association of cranial Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness.
- Secondary
 - ⇒ Brain tumors (especially craniopharyngioma) and cerebral metastasis
 - ⇒ Neurosurgery: usually after the removal of large adenomas
 - ⇒ Traumatic brain injury, pituitary bleeding, subarachnoid hemorrhage
 - ⇒ Pituitary ischemia (e.g., Sheehan syndrome, ischemic stroke)
 - ⇒ Infection (e.g., meningitis)
 - ⇒ Sarcoidosis

Wolfram's syndrome or the DIDMOAD syndrome is characterised by diabetes insipidus, diabetes mellitus, optic atrophy, and deafness

Causes of nephrogenic DI

- **Genetic:** two forms:
 1. **vasopressin-2 receptor (V2 ADH) mutation**
 - the more common form, **X linked** (usually **male** are affected)
 2. mutations in the aquaporin-2 gene → ↓ water reabsorption in the distal tubule.
 - less common form , autosomal recessive
- **Electrolytes:**
 - ⇒ hypercalcaemia
 - ⇒ hypokalaemia → desensitization of renal tubules to (ADH) → ↑ water excretion
- **Drugs:** the commonest precipitants
 - ⇒ **tetracycline** (demeclocycline)
 - ⇒ **lithium** → enters the principal cells of the collecting duct through the epithelial sodium channels (ENac) → **inhibits signalling pathways that involve glycogen synthase kinase type 3 beta (GSK3beta)** → dysfunction of aquaporin-2 water channel → nephrogenic DI.
- **Tubulo-interstitial disease:** obstruction, **sickle cell trait**, pyelonephritis, Sjögren's syndrome.
- **Pregnancy** (combined renal hyposensitivity to ADH, increased placental elimination of ADH, lowered thirst threshold and effect of fluid retention)

Hypokalaemia is a rare cause of polyuria and polydipsia

Nephrogenic DI is the most common adverse effect of lithium and occurs in up to 40% of patients

Features

- **Polyuria**
 - ⇒ urine output is > 50 ml/kg per day (3000 ml for a 60-kg female).
 - ⇒ Nocturia → Restless sleep, daytime sleepiness (**In the absence of nocturia, diabetes insipidus is very unlikely**)
- **Polydipsia**

Diagnosis

In suspected DI the most appropriate next investigation is → Urine and plasma osmolality (non-invasive first step)

- High plasma osmolality
 - ⇒ plasma osmolality **>305 mOsmol/kg**
 - ⇒ serum [Na] >145 mmol/L
- Low urine osmolality
 - ⇒ urine osmolality **<200 mOsm/kg**
 - ⇒ urinary [Na] 20-60 mmol/L
 - ⇒ urinary specific gravity <1.005.
- Water deprivation test with response to desmopressin (The patient is deprived of fluids for up to eight hours or 5% loss of body weight, following which desmopressin (DDAVP®) 2 micrograms (IM) is given).
 - ⇒ CDI → ↓ urine osmolality and ↑ serum osmolality **CORRECTED** by Desmopressin administration (plasma osmolality normalizes and urine osmolality rises).
 - ⇒ NDI → low urine osmolality and elevated serum osmolality, with **no significant response to desmopressin.**
- CT scan or MRI of the head: If CDI is diagnosed, to rule out brain tumors

Management

- Central DI
 - ⇒ Mild CDI (**urine output 3-4 litres/24 hours**) → increase oral water intake.
 - oral or nasogastric water is the replacement fluid of choice as this route provides a good buffer against rapid changes in serum sodium.
 - ⇒ If the urine output continues to be greater than 250 ml/hr → **Desmopressin** (Synthetic ADH) **is the drug of choice.**
- Nephrogenic DI → correct the underlying cause (e.g. stop the responsible drug)
 - ⇒ **Thiazide diuretic** (eg, hydrochlorothiazide), **amiloride** (K- sparing diuretic) → act on Distal Convoluted Tubule and inhibit the NaCl cotransporter and thus exaggerate the hypovolemia and increase an already activated renin–angiotensin–aldosterone system (RAAS) further. This mechanism stimulates proximal tubule sodium and water reabsorption resulting in less volume delivery to the collecting tubules where ADH work.
 - ⇒ **NSAIDs** (indomethacin) → inhibit prostaglandin synthesis, which has antagonistic effects on ADH.
 - ⇒ **Amiloride** is the drug of choice for lithium – induced nephrogenic DI → **blocks the epithelial sodium channel (ENac) in the collecting duct where lithium enters and causes DI.**

Rate of hypernatraemia correction

- Symptomatic patients with acute hypernatraemia (developed within 48h) → 5mmol/L in the first hour (or until symptoms improve) and is limited to 10mmol/L per 24h*
- No or mild symptoms → the rate of correction should not exceed 0.5mmol/L/h and is limited to 10mmol/L/24h.

Fluid status in DI

- Total body water: decrease
- Extracellular fluid: increase
- Intracellular fluid: decrease

DI → losing hypotonic fluid in the urine → ↑ osmolarity of the extracellular fluid → water will flow out of the intracellular compartment and into the extracellular compartment → ↑extracellular fluid volume and ↓intracellular fluid volume.

Which part of the nephron is most affected in diabetes insipidus?

Cortical and medullary collecting tubules

If there is hypovolaemic hypernatraemia ((hypotension, tachycardia, poor skin turgor)): The first step is to restore volume with isotonic fluids (0.9% saline).

Water deprivation test

Overview

- The diagnostic test to confirm DI is a water deprivation test.
- The goal of water restriction is to raise the plasma sodium to at least 145 mEq/L and plasma osmolality to 295 mOsmol/kg to stimulate enough ADH release to concentrate urine in normal subjects. If water restriction does not raise the Na and osmolality to this level, hypertonic saline infusion may be necessary.
- Normal plasma osmolality is 285-305 mosmol/kg.
- The normal 24-hour urine osmolality is, on average, 500-800 mOsm/kg of water.

Method

- Prevent patient drinking water (for a period of 8 h or until 5% of body weight is lost).
- Ask patient to empty bladder
- Patients should be weighed hourly.
- Test urine volume and osmolality every hour
- Test sodium and plasma osmolality every two hours
- Water deprivation continues until one of the following occurs:
 1. Urine osmolality rises and reaches a normal value (> 600 mOsmol/kg) → DI ruled out and **primary polydipsia** confirmed
 - Where urine osmolality reaches levels above 600 mOsmol/kg without desmopressin, then the diagnosis is **primary polydipsia**.
 2. No change in urine osmolality despite a rising plasma osmolality (> 290 mOsmol/kg)
 3. Plasma osmolality > 295–300 mOsmol/kg or sodium ≥ 145 meq/L
- In the latter two situations → **administer desmopressin** (a synthetic ADH analog) 2 µg intramuscular
 - ⇒ Monitor urine osmolality testing every 30 minutes for 2 hours
 - In **CDI**: Urine osmolality rises (> 600) after desmopressin administration (renal ADH receptors are intact).
 - In **NDI**: Urine osmolality remains low after desmopressin administration (defective renal ADH receptors).

Classification of causes of diabetes insipidus on basis of water deprivation and DDAVP® response

	Primary polydipsia (psychogenic polydipsia)	CDI	NDI
Lab findings on presentation	<ul style="list-style-type: none"> • Hyponatremia (< 137 meq/L) • Plasma osmolality: low- normal (255–280 mOsmol/kg) • Very low urine osmolality (< 250 mOsmol/kg) 	<ul style="list-style-type: none"> • Mild hypernatremia (> 150 mEq/L) • High-normal plasma osmolality (280–290 mOsmol/kg) or slightly elevated • Low urine osmolality <ul style="list-style-type: none"> ⇒ Partial DI: 300–500 mOsmol/kg ⇒ Complete DI: < 300 mOsmol/kg 	
Water deprivation test results	<ul style="list-style-type: none"> • Plasma osmolality: normal (275–290 mOsmol/kg) • Urine osmolality: rises, reaches normal value (> 600 mOsmol/kg) This result shows that both ADH release and effect are intact. 	<ul style="list-style-type: none"> • Plasma osmolality: rises (> 290 mOsmol/kg) • Urine osmolality: no change 	
Desmopressin administration results	<ul style="list-style-type: none"> • Water deprivation test results confirm diagnosis; no need to administer desmopressin 	<ul style="list-style-type: none"> • Plasma osmolality: normalizes (275–290 mOsmol/kg) • Urine osmolality rises 	<ul style="list-style-type: none"> • Plasma osmolality remains elevated • Urine osmolality remains low

Classification of causes of diabetes insipidus on basis of water deprivation and DDAVP® response

Urine osmolality after fluid deprivation (mOsm/kg)	Urine osmolality after DDAVP® (mOsm/kg)	Likely diagnosis
<300	>800	Cranial DI
<300	<300	Nephrogenic DI
>800	>800	Primary/psychogenic polydipsia
<300	>800	Partial cranial DI or nephrogenic DI or PP or diuretic abuse

A dramatic improvement in the ability of the kidneys to concentrate urine following the administration of DDAVP points towards a diagnosis of cranial diabetes insipidus

Differentiate psychogenic polydipsia from CDI and NDI:

- Patients with this disorder ingest and excrete up to 6L of fluid/day and are often emotionally disturbed.
- **Unlike patients with CDI and NDI, they do not have nocturia, nor does increased thirst wake them at night.**
- Patients with **acute psychogenic** polydipsia can concentrate their urine during a water deprivation test but chronic water intake diminishes medullary tonicity in the kidney.
- Patients with **long-standing polydipsia** are not able to concentrate their urine to maximal levels during water deprivation, a response similar to that of patients with partial central diabetes insipidus.

- However, unlike central diabetes insipidus, patients of psychogenic polydipsia show no response to exogenous ADH after water deprivation. This response resembles nephrogenic diabetes insipidus, but ADH levels are low in psychogenic polydipsia and high in nephrogenic polydipsia.

Polyuria

Definition

- defined as a urine output exceeding 3 L/day

Causes

Common (>1 in 10)	Infrequent (1 in 100)	Rare (1 in 1000)	Very rare (<1 in 10 000)
<ul style="list-style-type: none"> diuretics, caffeine & alcohol diabetes mellitus lithium heart failure 	<ul style="list-style-type: none"> hypercalcaemia hyperthyroidism 	<ul style="list-style-type: none"> chronic renal failure primary polydipsia hypokalaemia 	<ul style="list-style-type: none"> diabetes insipidus

Thiazide diuretic abuse

- polyuria and polydipsia of recent onset + high calcium, glucose and hypokalaemia, with an elevated bicarbonate. ↑ Serum Osmolality > 300

Hyponatraemia (serum sodium less than 135 mEq/L).

Prevalence

- Occurs in up to 30% of hospitalised patients

Classifications

- based on severity:
 - ⇒ Mild hyponatraemia : serum sodium between 130 and 135 mmol/l
 - ⇒ Moderate hyponatraemia: serum sodium between 125 and 129 mmol/l
 - ⇒ Profound hyponatraemia: serum sodium <125 mmol/l
- based on time of development:
 - ⇒ **Acute** hyponatraemia: hyponatraemia that is documented to exist < 48 h.
 - ⇒ **Chronic** hyponatraemia: hyponatraemia that is documented to exist ≥ 48 h.
 - If hyponatraemia cannot be classified, we consider it being chronic

Mechanisms of causes

1. water excess
2. sodium depletion
3. Pseudohyponatraemia: (isotonic hyponatraemia)
 - ⇒ Causes
 - Hyperglycaemia
 - hyperlipidaemia (increase in serum volume)
 - hyperproteinemia (e.g. myeloma)
 - taking blood from a drip arm.
 - ⇒ exclude hyperglycaemic hyponatraemia by measuring the corrected serum Na⁺

- adding 2.4 mmol/l to the measured serum sodium for every 5.5 mmol/l incremental rise in serum glucose concentration above a standard serum glucose concentration of 5.5 mmol/l.
 - corrected $\text{Na}^+ = \text{measured } \text{Na}^+ + 2.4 \times (\text{serum glucose mmol} - 5.5 / 5.5 \text{ mmol})$
- ⇒ Non-hypotonic hyponatraemia does not cause brain oedema and is managed differently from hypotonic hyponatraemia.

Pseudohyponatraemia is characterised by a normal **measured serum osmolarity**, however the **calculated osmolarity** (based on an erroneously low plasma sodium result) is reduced. This results in a **raised osmolar gap**

Causes of hyponatraemia

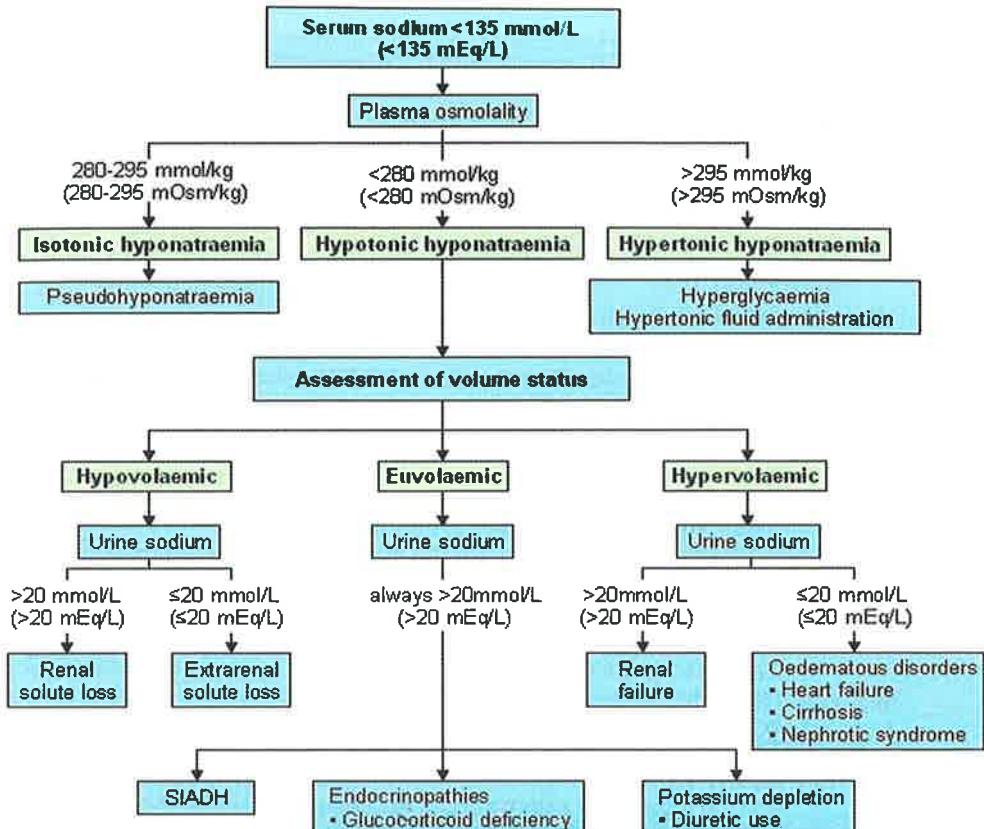
Urinary sodium > 20 mmol/l		Urinary sodium < 20 mmol/l	
Sodium depletion, renal loss (patient often hypovolaemic)	Patient often euvolaemic	Sodium depletion, extra-renal loss (hypovolaemic)	Water excess (patient often hypervolaemic and oedematous)
<ul style="list-style-type: none"> • diuretics • diuretic stage of renal failure • Addison's 	<ul style="list-style-type: none"> • SIADH (urine osmolality > 500 mmol/kg) • hypothyroidism 	<ul style="list-style-type: none"> • diarrhoea, vomiting, sweating • burns, adenoma of rectum 	<ul style="list-style-type: none"> • secondary hyperaldosteronism: heart failure, cirrhosis • reduced GFR: renal failure • IV dextrose, • psychogenic polydipsia

Features

- Fatigue, Muscle weakness
- Gait disturbance, Falls
- Cerebral oedema → Disorientation, Seizures

Investigations

- **Urinary sodium** and **osmolarity** levels aid making a diagnosis.
 - ⇒ urinary sodium
 - Reduced urinary sodium excretion [less than 30 mmol/l] may indicate total body sodium depletion even if plasma sodium levels are normal.
 - may be misleading in the presence of renal impairment or diuretic therapy.



Management

- ascertain volume status as this will determine management.
 - ⇒ **Hypovolaemic hyponatraemia**
 - Diagnosis may supported by an **elevated urea suggesting dehydration**.
 - rehydration with **sodium chloride 0.9%** or a balanced crystalloid (Hartmann's)
 - avoid rapid Na correction to reduce the risk of central pontine myelinolysis.
 - The rate of Na correction should not exceed **8 mEq/L per day**.
 - ⇒ **Euvolaemic hyponatraemia**
 - check urine and serum osmolality. Does the patient meet the criteria for SIADH?
 - treat the underlying cause where possible in SIADH
 - fluid restriction (500-750mls/day)
 - monitor fluid balance and perform daily weights
 - consider **demeclocycline** or tolvaptan (under specialist supervision). Both inhibit the action of antidiuretic hormone.
 - ⇒ **Hypervolaemic hyponatraemia**
 - fluid and salt restriction
 - consider diuretics
 - treat the underlying cause (e.g. cardiac failure)

Hyponatraemia: correction

Acute hyponatraemia is that which occurs within a duration of 48 hours.

Acute hyponatraemia

- predisposing factors to acute hyponatraemia:
 - ⇒ Over consumption of fluids,
 - ⇒ Post-operative hyponatraemia is not uncommon and is likely to be due to a combination of SIADH which develops in the post-op period and the infusion of inappropriate IVIs.
 - ⇒ prolonged race duration and inadequate training
- Pathophysiology
 - ⇒ When hyponatraemia develops over a short duration the ability of the brain to adapt is exceeded and cerebral oedema can result which may lead to confusion, seizures and coma. As a result, patients may die from brain herniation.
- Features
 - ⇒ hyponatraemic encephalopathy which is life threatening and presented with a fit.
- Treatment of **Hyponatraemia with severe symptoms**
 - ⇒ **Hypertonic saline (3%) boluses are the most appropriate treatment to improve neurological status in such patients.**
 - 150mls of 3% hypertonic saline over 20 mins
 - check the serum sodium after 20min while repeating an infusion of 150ml 3% hypertonic saline for the next 20min.
 - repeat therapeutic twice or until a target of 5mmol/l increase in serum sodium is achieved
 - **The target sodium by which one should elevate the sodium is 5 mmol/l over the first hour.**
 - limit the increase in serum sodium to a total of 10mmol/l during the first 24h and an additional 8mmol/l during every 24h thereafter until the serum sodium concentration reaches 130mmol/l
 - ⇒ Decompressive craniotomy would help alleviate raised intracranial pressure due to cerebral oedema however is not an appropriate first line treatment.

Hypopituitarism

Definition

- Deficiency of one or more anterior pituitary hormones.
 - ⇒ GH deficiency → growth retardation (during childhood), ↓ bone density, muscle atrophy, hypercholesterolemia
 - ⇒ Prolactin deficiency → lactation failure following delivery
 - ⇒ FSH/LH deficiency → hypogonadotropic hypogonadism (secondary hypogonadism)
 - ⇒ TSH deficiency → secondary hypothyroidism
 - ⇒ ACTH deficiency → secondary adrenal insufficiency
- Hypopituitarism becomes symptomatic when more than 80% of pituitary cells are damaged.

Causes

- Intrasellar/parasellar masses
 - ⇒ Nonsecretory pituitary macroadenomas (≥ 10 mm in diameter) are the most common cause of hypopituitarism among adults ($\sim 40\%$ of cases).
 - ⇒ Less common: internal carotid artery aneurysms, meningiomas, craniopharyngiomas,
- Pituitary apoplexy
 - ⇒ results in acute hypocortisolism and hypothyroidism, can present with sudden hypotension and hypovolemic shock
- Sheehan syndrome: postpartum necrosis of the pituitary gland. Usually occurs following postpartum hemorrhage but can also occur even without clinical evidence of hemorrhage.
- Traumatic brain injury (especially around the skull base)
- Infiltration of the pituitary and/or hypothalamus
 - ⇒ Hemochromatosis, Sarcoidosis
 - ⇒ Infections: meningitis, TB
- Empty sella syndrome
- Iatrogenic
 - ⇒ Hypophysectomy
 - ⇒ Pituitary irradiation
- Congenital
 - ⇒ deficiency of hypothalamic hormones: GnRH deficiency (Kallman syndrome)

Features (depends on which hormone is deficient).

- Growth hormone deficiency: The first hormone to fall is the growth hormone
 - ⇒ in children → short stature
 - ⇒ in adults → tiredness, weight gain
- ACTH deficiency → weight loss, weakness, Postural hypotension, chronic hyponatremia, hypoglycemia
- TSH deficiency → weight gain, cold intolerance, lethargy, constipation, dry skin
- FSH/LH deficiency
 - ⇒ Women → primary amenorrhea (delayed puberty), secondary amenorrhea, irregular menstrual cycles, infertility
 - ⇒ The presence of regular menstrual cycles in women rules out hypogonadism.
 - ⇒ Men → delayed puberty, loss of libido, infertility, testicular atrophy.
- Intrasellar/parasellar masses (e.g., pituitary macroadenomas, craniopharyngiomas) can manifest with headache, visual field defects (bitemporal hemianopsia), and/or diplopia
- Pituitary apoplexy → Severe headache, bilateral hemianopia, diplopia (due to damage to CN III), sudden hypotension.
- PRL deficiency is rare, except in Sheehan's syndrome → failure of lactation
- Houssay phenomenon: Amelioration of diabetes mellitus in patients with hypopituitarism due to reduction in counter-regulatory hormones.

In the majority of cases, the development of hypopituitarism follows a characteristic order, with secretion of GH, then gonadotrophins being affected first, followed by **TSH** and **ACTH** secretion at a later stage.

Investigations

- **Insulin stress test**
 - ⇒ the gold standard dynamic test for the diagnosis of ACTH and GH deficiency in patients with suspected hypopituitarism.
 - ⇒ a weight-based dose of intravenous insulin to achieve a hypoglycaemia level below 2.2 mol/l. With normal pituitary function GH and cortisol should rise
 - ⇒ **Contraindications:** epilepsy, ischaemic heart disease and adrenal insufficiency
- central/secondary adrenal insufficiency: low morning cortisol level + Low to normal ACTH
- thyroid function tests → secondary hypothyroidism: ↓ or normal TSH with ↓ serum free T4 and ↓ serum free T3
- MRI brain

Management

- **Hydrocortisone:** the most important replacement therapy to be started first to avoid the possibility of precipitating an adrenal crisis.
 - ⇒ Fludrocortisone is only necessary in patients with adrenal insufficiency who are unable to maintain normal blood pressure control.
- **Thyroxine replacement:** should be begun after commencing hydrocortisone because levothyroxine increases the clearance of cortisol and may precipitate an adrenal crisis.
- **GH therapy:** licensed for treatment of symptoms with reduced quality of life on adult growth hormone deficiency assessment (AGHDA) questionnaire score.
- **Testosterone:** the most appropriate treatment to prevent the progression of bone loss
- In addition to pituitary hormone replacement, the underlying cause of hypopituitarism should be treated.

Patients with TSH deficiency should not be treated with levothyroxine until ACTH deficiency has been ruled out and/or treated because levothyroxine increases the clearance of cortisol and may precipitate an adrenal crisis

Growth hormone (GH)

Secretion

- Hypothalamus → release Growth hormone releasing hormone (GHRH) → stimulates the somatotrophs in the **anterior pituitary gland** → release GH.
- Secreted in a pulsatile manner. **The highest level of GH is seen around midnight during the sleep period.**
- **GHRH uses two second messengers cAMP and IP₃/Ca²⁺** to stimulate growth hormone release.

Which signaling pathways does growth hormone (GH) use?

⇒ Tyrosine kinase receptor

Mechanism of action

- **Direct** action via **tyrosine kinase receptor** on target tissues, such as skeletal muscle, liver, or adipose tissue
 - ⇒ ↓ Glucose uptake into cells (↑ insulin resistance) → ↑ Blood insulin levels
 - ⇒ ↑ Lipolysis
 - ⇒ ↑ Protein synthesis in muscle
 - ⇒ ↑ Amino acid uptake
- **Indirect** action via insulin-like growth factor 1 (IGF-1), primarily secreted by the liver
 - ⇒ Growth stimulation
 - ⇒ Anabolic effect on body

Growth hormone (GH) counteracts in general the effects of insulin on glucose and lipid metabolism but shares protein anabolic properties with insulin.

GH along with cortisol and adrenalin (called counter-regulatory hormones) tell the body to increase the availability of glucose – so it counters the effect of insulin.

GH regulation

↑ GH secretion	↓ GH secretion
<ul style="list-style-type: none"> • Deep sleep • Fasting → Hypoglycaemia • Alpha adrenergic activity • Stress • Exercise • Ghrelin the "hunger hormone" • Amino acids (Arginine) • Sex steroids (estrogen or testosterone) • Puberty • CKD • Thyroid hormone, thyroxine • Estrogen, testosterone • Short-term glucocorticoid exposure 	<ul style="list-style-type: none"> • Somatostatin • Beta adrenergic activity • Hyperglycaemia (initially) • Obesity • Free fatty acids • Hypothyroidism • IGF-1 • Pregnancy • Increased age • Glucose • Chronic glucocorticoid therapy

- An **increase in GH levels is seen in patients with Type 1 DM**, while in patients with Type 2 DM the levels may be increased, normal or decreased.
- **GH levels increase in malnutrition** in contrast to a **decrease in IGF-1 levels**.
- In poorly controlled diabetics GH levels are invariably raised whilst normal or low levels of IGF-1 are found, indicating a dissociation between the two factors.

Conditions associated with GH disorders

- GH deficiency: resulting in short stature
- excess GH: acromegaly

Growth hormone deficiency (GHD)

Causes

- Pituitary tumours or their treatment, (e.g. surgery, cranial irradiation) is the most common cause.
- Any other cause of hypopituitarism (see hypopituitarism topic)

Features

- In infancy are **hypoglycemia** and micropenis is the primary manifestations
- In early childhood: growth failure is the primary manifestation. causes premature fusion of the epiphyseal portion of the bone.
- **In adults**
 - ⇒ ↑↑ fat mass
 - ⇒ ↓↓ lean body mass
 - ⇒ ↓↓ bone mineral density (BMD) → osteopenia/osteoporosis
 - ⇒ ↓↓ energy, ↓↓ quality of life (QoL)
 - ⇒ ↓↓ sweating → Dry skin
 - ⇒ ↑↑ greater mortality , ↑↑ cardiovascular risk
 - ⇒ ↑↑ insulin resistance
 - ⇒ Dyslipidaemia (\uparrow LDL).

Diagnosis

- Decreased serum insulin-like growth factor-1 (IGF-1) levels: **may be normal in up to 50%.**
- **Dynamic tests of GH secretion**
 - ⇒ **Insulin tolerance test (ITT): the gold standard for the diagnosis**
 - insulin-induced hypoglycaemia → GH response of less than 9 mU/L (3 ng/ml) → GHD
 - **Causes of false positive test:** Obesity → ↓ GH response to insulin → false positive test
 - **Contra-indications to ITT:**
 - ❖ seizures (eg: in epilepsy)
 - ❖ IHD, Abnormal ECG
 - ❖ basal cortisol levels <100 nmol/L
 - ❖ Glycogen storage disease
 - ❖ Elderly (due to high risk of hypoglycaemia)
 - ⇒ **Alternative test if ITT is contraindicated:**
 - arginine-GHRH stimulation test
 - glucagon-GH-releasing hormone stimulation test
- **Two tests of GH stimulation test are required** before making the diagnosis.

Treatment → Subcutaneous injections of recombinant human growth hormone.

- **Criteria for GH treatment:** only if **all the following three criteria are met**
 1. Severe GH deficiency, defined as a **peak GH response of less than 9 mU/litre (3 ng/ml)** during an insulin tolerance test.
 2. Impairment of **Quality of Life (QoL)**: 'Quality of life assessment of growth hormone deficiency in adults' (QoL-AGHDA) score ≥ 11 .
 3. Treatment for other pituitary hormone deficiencies

Adverse effects of GH replacement

- Sodium and water retention
 - ⇒ Weight gain
 - ⇒ Carpal tunnel syndrome
- Hyperinsulinaemia
- Arthralgia (possibly due to intra-articular cartilage swelling)
- Myalgia
- **Benign intracranial hypertension** (resolves on stopping treatment)

Contraindications to GH replacement

- Active malignancy
- Benign intracranial hypertension
- Pre-proliferative/proliferative retinopathy in diabetes mellitus

Which treatment is most appropriate for patients with preserved pituitary function and deficiencies in growth hormone (GH) and adrenocorticotropic hormone (ACTH)?

- **Cortisol replacement therapy only.**
 - ⇒ GH deficiency can be caused by hypoadrenalism. Concomitant cortisol and GH replacement therapies are not appropriate because cortisol alone may be sufficient to restore GH secretion.

MRCP-UK, SCE .Sample question

patients with childhood-onset GHD who are candidates for GH therapy after adult height achievement. What is the most appropriate next step in management?

→ should be retested for GHD

Acromegaly

Approximately 30% of growth hormone (GH) secreting pituitary tumours is associated with mutation of the Gs protein alpha subunit

Definition

- Acromegaly is the clinical condition resulting from prolonged excessive GH and hence IGF-1.

Epidemiology

- Most cases are diagnosed at 40–60 years.

Causes

- Pituitary adenoma (95%)
- ectopic GHRH or GH production by tumours e.g. pancreatic
 - ⇒ mechanism: GH secreting tumours → **mutation in the alpha sub-unit of the stimulatory guanosine triphosphate (GTP) binding protein** → persistent **elevation of cyclic adenosine monophosphate (cAMP)** → production of excess growth hormone.

Features

- Headaches
- Visual field loss (attributable to optic chiasmal compression), diplopia (due to cranial nerve palsy)
- Increase in shoe size
- **Increased sweating : due to sweat gland hypertrophy**
- Hands: spade-like hands
- Face: general coarse facial appearance, prognathism, eyes, bitemporal hemianopia
- Mouth: large tongue → Sleep apnea, interdental spaces

Macroglossia: Causes

- Hypothyroidism
- **Acromegaly**
- Amyloidosis
- Duchenne muscular dystrophy
- Mucopolysaccharidosis (e.g. Hurler syndrome)
- Down's syndrome

Complications

- Hypertension (40%).
- Insulin resistance and impaired glucose tolerance (40%)/diabetes mellitus (20%).
- Obstructive sleep apnoea: due to soft tissue swelling in nasopharyngeal region.
- ↑ risk of colonic polyps and colonic carcinoma
- ↑ Ischaemic heart disease and cerebrovascular disease.
- ↑ Congestive cardiac failure and possible ↑ prevalence of regurgitant valvular heart disease.
- Cardiomyopathy → heart failure
- Osteoarthritis, Arthralgia, **Pseudogout**
- Carpal tunnel syndrome: Positive Tinel's sign
- 6% of patients have MEN-1, hypercalcemia → primary hyperparathyroidism → MEN 1.

Investigations

The diagnostic test for acromegaly is an oral glucose tolerance with growth hormone measurements

- Serum insulin-like growth factor 1 (IGF-1)
 - ⇒ **IGF-1 measurement is the most appropriate initial investigation**
 - ⇒ May also be used as a screening test, sometimes used to **monitor** disease
 - ⇒ Normal IGF-1 levels rule out acromegaly
 - ⇒ If ↑ IGF-1 → conduct OGTT with baseline GH → measure GH after 2 hours:
 - if GH suppressed → acromegaly ruled out
 - if GH not suppressed: confirmed acromegaly → conduct pituitary MRI
 - ⇒ Growth hormone (GH) levels vary during the day and are therefore not diagnostic.
- Oral glucose tolerance test (OGTT) with serial GH measurements.
 - ⇒ **The definitive test**
 - ⇒ Lack of suppression of GH to < 1 µg/L following documented hyperglycemia during an oral glucose load.
 - ⇒ False +ves: Chronic renal and liver failure, malnutrition, diabetes mellitus, heroin addiction, adolescence (due to high pubertal GH surges).

- Assess for other pituitary functions
- **Pituitary MRI:** usually demonstrates the tumour (98%)
- If no pituitary tumor detected → serum GHRH + radiology of the chest and abdomen to detect ectopic GHRH-secreting tumor (usually a GHRH-secreting carcinoid of lung or pancreas.)

- **Associated laboratory features**
 - ⇒ **Serum calcium:** GH stimulates renal 1 α -hydroxylase → ↑ 1,25-Dihydroxycholecalciferol (DHCC) → hypercalcaemia → hypercalciuria (which occurs in 80%) → ↑ likelihood of renal stones.
 - ⇒ elevated **Phosphate levels**
 - ⇒ Raised prolactin in 1/3 of cases → galactorrhoea

In active acromegaly with associated diabetes mellitus → There is insulin resistance

Acromegaly → ↑ risk of colon cancer → regular colonoscopy screening, starting at the age of 40 years.

Management

Trans-sphenoidal surgery is first-line treatment for acromegaly in the majority of patients

Octreotide can be used as an adjunct to surgery in patients with acromegaly

- **Surgery: transsphenoidal adenomectomy**
 - ⇒ **first-line treatment for acromegaly in the majority of patients**
 - ⇒ **the percentage likelihood of cure from surgery:** > 85% for microadenomas and **40–50% for macroadenomas**
- **Medication:** In patients with **inoperable tumors** or **unsuccessful surgery**, medication and radiotherapy are indicated to reduce tumor size and limit the effects of GH and IGF-1.
 - ⇒ Somatostatin analogs (e.g., octreotide, lanreotide, pasireotide)
 - **first line medical therapy.**
 - side effects: gallstone disease
 - ⇒ **Dopamine agonists** (e.g., **bromocriptine**, cabergoline):
 - **less effective** than somatostatin analogues.
 - may be helpful if there is coexistent secretion of PRL → significant tumour shrinkage.
 - Cabergoline is more effective than bromocriptine
 - ⇒ **GH receptor antagonists** (e.g., **pegvisomant**)
 - Indicated for somatostatin non-responders. **Third-line treatment when surgery, radiotherapy and somatostatin analogues are not effective.**
 - Very effective - decreases IGF-1 levels in 90% of patients to normal
 - Pre-operative: may improve metabolic risk factors for surgery, such as hypertension and hyperglycaemia
 - Monitoring: liver function tests → discontinue pegvisomant if the transaminases are greater than 3-fold elevated.

- **Radiotherapy**

- ⇒ Indications: residual tumor mass following surgery, and if medical therapy is unavailable, unsuccessful, or not tolerated.
- ⇒ stereotactic radiotherapy (SRT) is preferred over conventional radiation therapy
- ⇒ Side effects: Danger of hypopituitarism → do annual hormonal testing

Long acting somatostatin analogue

- **Mode of action** → ↓ meal-time related superior mesenteric artery blood flow
- One intra-muscular injection should be given every 14 days.
- **Common side effects** : pain at injection site, GIT disturbances , Cholelithiasis, Sinus bradycardia , Hypoglycaemia, hyperglycaemia

Which test is the best way to monitor for recurrence after trans-sphenoidal surgery for resection of a growth hormone-secreting pituitary adenoma?

- Insulin-like growth factor 1(IGF-1)

Prognosis

- Left ventricular failure is the most common cause of death if treatment is unsuccessful

Laron's syndrome

Definition

- an autosomal recessive disorder characterized by an **insensitivity to (GH)**, usually caused by a mutant growth hormone receptor.

Features

- short stature
- **Reduced risk of developing acne, cancer and diabetes mellitus type II.**
- Seizures are frequently seen secondary to hypoglycemia.
- low levels of insulin-like growth factor (IGF-1) and its principal carrier protein, insulin-like growth factor binding protein 3.

Treatment

- injections of recombinant IGF-1.
- Not respond to growth hormone treatment due to a lack of GH receptors.

Nelson syndrome (post adrenalectomy syndrome)

Aetiology

- bilateral adrenalectomy in patients with a previously undiscovered pituitary adenoma
- occurs in 30% of **patients adrenalectomised for Cushing's disease.**

Pathophysiology

- Bilateral adrenalectomy → no endogenous cortisol production → no negative feedback from cortisol on hypothalamus → increased CRH production → uncontrolled enlargement of preexisting ACTH-secreting pituitary adenoma → increased secretion of ACTH and melanocyte-stimulating hormones (MSH) → symptoms of pituitary adenoma and ↑ MSH.

Features

- Headaches, bitemporal hemianopia (mass effect)
- Cutaneous **hyperpigmentation**: arises from the MSH products of the proteolysis of POMC, which also produces ACTH.

Diagnosis

- **High levels of beta-MSH and ACTH**
- Pituitary adenoma on MRI confirms the diagnosis.

Treatment

- Surgery (e.g., transsphenoidal resection) and/or pituitary radiation therapy (e.g, in the case of tumor residues after surgery)

Monitoring

- ACTH levels
- serial pituitary imaging.

Pituitary adenoma

Epidemiology

- Small pituitary tumours (<4 mm) are common and have been reported in up to **10% of MRIs in the general population**.
- Only a small fraction of such tumours are associated with clinical features suggestive of pituitary disorder.

Classifications

- According to size:
 - ⇒ Microadenoma: ≤ 10 mm
 - ⇒ Macroadenoma: > 10 mm
- According to hormone secretion
 - ⇒ **Secretory pituitary adenomas (60%):** hormone secretion → hyperpituitarism
 - Lactotroph adenoma: Prolactinoma 35–40%.
 - Somatotroph adenoma: Growth hormone (acromegaly) 10–15%.
 - Corticotroph: ACTH adenoma (Cushing's disease) 5–10%.
 - Thyrotroph: TSH adenoma <5%
 - ⇒ **Non-secretory pituitary adenomas 'chromophobe'** : Non-functioning 30–35%.
 - Which **nonfunctioning pituitary adenoma subtype** is characterized by a **high recurrence rate, invasion, and increased risk of hemorrhagic infarction?**
 - ⇒ **Corticotroph adenoma**

Prolactinomas are the most common pituitary adenomas

Features: depends on the tumor **size** and whether the tumor **produces** hormones

- **Secretory microadenomas** → hyperpituitarism according to which hormone is secreted
- **Secretory macroadenomas** → hyperpituitarism + **mass effects** - (e.g., headache, **bitemporal hemianopsia**, diplopia)
- **Non-secretory microadenomas** → **Asymptomatic**
- **Non-secretory macroadenomas** → **Hypopituitarism + mass effects** (e.g., headache, bitemporal hemianopsia, diplopia)

- **Mass effects**

- ⇒ **Superior extension** → firstly compression of the optic apparatus and later the hypothalamus.
- ⇒ **Lateral extension** → compression or invasion of the cavernous sinus can compromise third, fourth, or sixth cranial nerve functions, manifest as diplopia in 5 to 15% of pituitary tumour patients.

The presence of an **elevated prolactin level** along with **secondary hypothyroidism** and **hypogonadism** is indicative of **stalk compression due to pituitary adenoma**

Diagnostics

- Hormone assays
 - ⇒ Basal prolactin levels
 - ⇒ Insulin-like growth factor-1 (IGF-1)
 - ⇒ 24-hour urine cortisol
 - ⇒ Thyroid function tests
- Cranial contrast MRI (initial test) : reveals an intrasellar mass
 - ⇒ CT scan may be considered
- Perimetry: to assess visual field defects

Treatment

- **Non-secretory pituitary microadenomas** (incidentalomas) → no treatment (only follow-up with serial MRI)
- **Prolactinomas** (PRL is usually $>6000\text{mU/ml}$)
 - ⇒ First-line: dopamine agonists (e.g., cabergoline, bromocriptine) → shrink pituitary adenoma.
 - ⇒ Second-line: trans-sphenoidal hypophysectomy ± adjuvant radiotherapy
- **Other pituitary adenomas**
 - ⇒ First-line: transsphenoidal hypophysectomy
 - ⇒ Second-line: Medications ± pituitary irradiation

Differentiate between non-functioning adenoma and macroadenoma:

- Although stalk compression with a non-functioning tumour may cause hyperprolactinaemia the concentrations of prolactin are usually below 2000 mU/L and galactorrhoea would be rare.

Except Prolactinomas, all other functioning adenomas are treated primarily by surgery (i.e.; for secondary hyperthyroidism, acromegaly etc).

If the CT scan shows a pituitary tumour with suprasellar extension, which structures is likely to be compressed?

- **Optic chiasm**
 - ⇒ The optic chiasm lies 5-10 mm above the diaphragm sellae and anterior to the stalk.
 - ⇒ Adenomas $> 1.5\text{ cm}$ frequently have suprasellar extension, and the MRI will show compression and upward displacement of the optic chiasm.

Pituitary Incidentaloma

- Asymptomatic, pituitary tumors that are detected on MRI or CT scans done for other reasons without hormonal hyper- or hyposecretion and has a benign natural history.
- The most appropriate strategy → observation and repeat scanning.

Pituitary apoplexy

Sudden-onset retro-orbital headache, vomiting, visual disturbance and hormonal dysfunction should lead you to consider a diagnosis of pituitary apoplexy

Definition

- Sudden hemorrhage into the pituitary gland. Most commonly occurs in patients with a preexisting pituitary adenoma which may be asymptomatic before presentation.

Predisposing factors

- pituitary adenomas (most common)

Features

- Features of raised intracranial pressure ($\uparrow\uparrow$ ICP)
 - ⇒ Sudden-onset retro-orbital headache, similar to that seen in subarachnoid haemorrhage
 - ⇒ vomiting
 - ⇒ **visual disturbance:** diplopia due to pressure on the oculomotor nerves
- Features of pituitary insufficiency
 - ⇒ The main **initial problem** is $\downarrow\downarrow$ ACTH, → $\downarrow\downarrow$ cortisol → features of an 'Addisonian crisis', i.e. **hypotension, hyponatraemia**, hyperkalaemia and hypoglycaemia.
 - ⇒ Subacutely, there can be \downarrow TSH and gonadotropins (LH and FSH).

Diagnosis

- Magnetic resonance imaging

Treatment

- Urgent steroid replacement
- Indications for neurosurgical decompression:
 - ⇒ **severe neuro-ophthalmic signs** (e.g. severely reduced visual acuity, severe and persistent or deteriorating visual field defects or deteriorating level of consciousness)
 - ⇒ Ocular paresis because of **involvement of III, IV or VI cranial nerves** in the cavernous sinus in the absence of visual field defects or reduced visual acuity **is not an indication for immediate surgery.** Resolution will typically occur within days or weeks with conservative management
- Over the long-term → corticosteroid, testosterone and thyroid hormone replacement.

Prognosis

- Nearly **80%** of the patients will need some form of **hormone replacement** after apoplexy.
 - ⇒ **Growth hormone deficiency is the most commonly observed** deficit after apoplexy and is present in almost all patients but rarely replaced.

Hyperprolactinaemia

The first test to do when seeing anyone with hyperprolactinaemia is to exclude pregnancy, as it is the most common cause.

Prolactin hormone overview

- Secreted by lactotrophic cells of the anterior pituitary gland
- Effects on females:** ↑ breast tissue growth and lactation, ↓ ovulation, ↓ GnRH secretion, amenorrhea, galactorrhea, ↓ libido
- Effects on males:** ↓ spermatogenesis and ↓ libido.
- Stimulated by thyrotropin-releasing hormone (TRH)
- Inhibited by hypothalamic **dopamine** and γ-aminobutyric acid (GABA).

Epidemiology

- Hyperprolactinemia is the most common form of hyperpituitarism.**
- Post-mortem studies show microadenomas in 10% of the population.
- Microprolactinomas are commoner than macroprolactinomas
- More common in females

Pathophysiology

Prolactin → ↓ GNRH → hypogonadotropic hypogonadism (↓ LH and FSH → ↓ estrogen, ↓ testosterone)

Which hormones are expected to be low in hyperprolactinaemia?

- Hyperprolactinaemia suppresses the release of gonadotropin-releasing hormone (**GRH**), which leads to reduced production of luteinising hormone (**LH**) and follicle-stimulating hormone (**FSH**).

Causes

Causes of raised prolactin – the Ps

- * **pregnancy**
- * **prolactinoma**
- * **physiological**
- * **polycystic ovarian syndrome**
- * **primary hypothyroidism**
- * **Phenothiazines, metoclopramide, domperidone**

- Physiological: Pregnancy**, Sexual intercourse, Nipple stimulation/suckling, Stress.
- Pituitary tumour:**
 - ⇒ **Prolactinomas. the most common cause (~ 50%) of pathological hyperprolactinemia**
 - Microprolactinoma → prolactin level usually of 1,000-3,000 mU/L.
 - Macroprolactinoma: prolactin level usually greater than 3000 mU/L.

- ⇒ Mixed GH/PRL-secreting tumour. **Acromegaly (1/3 of patients)**
- ⇒ Macroadenoma compressing stalk.
- ⇒ Empty sella.
- ⇒ Multiple endocrine neoplasia (MEN): Occur in 20% of patients with MEN-1 (prolactinomas are the commonest pituitary tumour in MEN-1). **MEN type 1 should be considered in presentation with microprolactinoma and recurrent dyspepsia** (gastrinomas, insulinomas, carcinoid).
- **Hypothalamic disease:** mass compressing stalk (craniopharyngioma, meningioma, neurofibromatosis).
- **Infiltration :** sarcoidosis, Langerhans cell histiocytosis.
- **Stalk section:** head injury, surgery.
- **Cranial irradiation.**
- **Drug induced:** → ↓dopamine release → ↓dopamine inhibition effect on prolactin → ↑ prolactin release. (**Levels less than 1000 are most likely to be drug related**)
 - ⇒ Dopamine receptor antagonists (**metoclopramide most common**, domperidone).
 - ⇒ Neuroleptics (perphenazine, flupentixol, fluphenazine, **haloperidol**, thioridazine, **chlorpromazine**, trifluoperazine, **risperidone**, sulpiride).
 - ⇒ Antidepressants (tricyclics, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, sulpiride, amisulpride, imipramine, clomipramine, amitriptyline, pargyline, clorgiline).
 - ⇒ Cardiovascular drugs — verapamil, methyldopa, reserpine.
 - ⇒ Opiates
 - ⇒ Cocaine
 - ⇒ Protease inhibitors — e.g. ritonavir, indinavir, zidovudine. • Oestrogens. • Others— bezafibrate, omeprazole, H2 antagonists.
- **Metabolic:**
 - ⇒ **Hypothyroidism: TRH increases PRL.**
 - ⇒ **Chronic renal failure: reduced PRL clearance.**
 - ⇒ Severe liver disease — disordered hypothalamic regulation.
- **Other:**
 - ⇒ Polycystic ovarian syndrome (PCOS): can make differential diagnosis of menstrual problems difficult.
 - ⇒ Chest wall lesions—zoster, burns, trauma (stimulation of suckling reflex).
 - ⇒ Temporal lobe seizures, due to close proximity to the hypothalamus.
- **No cause found: 'Idiopathic' hyperprolactinaemia.**
- **Macroprolactinemia ('big' PRL)**
 - ⇒ aggregates of prolactin and antibodies (in particular, antipro lactin autoantibodies) that range in size from approximately 150 to 170 kilo Dalton (kD). The most common form of native prolactin in serum is 23 kD in size
 - ⇒ These complexes are **immunologically detectable but not biologically active**, so they appear to cause no clinical abnormality. **Typically, there is hyperprolactinaemia with regular ovulatory menstrual cycles.**

- ⇒ Can be misdiagnosed and treated as prolactin hypersecretion
- ⇒ Detection
 - Misdiagnosis can be avoided by asking the laboratory to **pretreat the serum with polyethylene glycol** to precipitate the macroprolactin before the immunoassay for prolactin.
 - Gel filtration chromatography (gold standard).

Quetiapine, clozapine, aripiprazole, and olanzapine are antipsychotics, with little or no effect on prolactin (lower binding affinity to D2 receptors).

Cranial irradiation may initially cause hyperprolactinaemia but a low PRL is typical after a year.

A patient presented with **elevated oestradiol** and **prolactin** with suppressed (LH/FSH) and recent amenorrhoea. what is the most likely diagnosis?

- **Pregnancy**

Features of excess prolactin

- Hyperprolactinaemia (microadenomas and macroadenomas)
 - ⇒ Men: impotence, loss of libido, erectile dysfunction, rarely galactorrhoea
 - ⇒ Women: amenorrhoea, galactorrhoea, reduced libido
- Mass effects (macroadenomas only):
 - ⇒ Headaches and visual field defects (uni- or bitemporal field defects).
 - ⇒ Hypopituitarism.
 - ⇒ Invasion of the cavernous sinus may lead to cranial nerve palsies.
- Long-term risk of d ↓BMD.

Investigations

- **Serum prolactin (PRL)**
 - ⇒ stress of venepuncture may cause mild hyperprolactinaemia, so **2–3 levels should be checked**, preferably through an indwelling cannula after 30min
 - ⇒ Serum PRL <2,000mU/L is suggestive of a microprolactinoma or a non-functioning macroadenoma compressing the pituitary stalk.
 - ⇒ Serum PRL >4,000mU/L is diagnostic of a macroprolactinoma.
 - ⇒ **Hook effect:**
 - Very high prolactin concentrations can interfere with immunoassay systems resulting in falsely low prolactin determination. this is due to "hook effect" which describes the inhibition of immune complex formation by excess antigen concentrations.
 - this is an important consideration in patients with large pituitary adenomas when the clinical suspicion of prolactinoma is strong, as in patients with amenorrhoea-galactorrhoea or longstanding hypogonadism.
 - appropriate dilution of the serum in such cases helps in accurate estimation of serum prolactin concentration.
- **Thyroid function and renal function:** Hypothyroidism and chronic renal failure are causes of hyperprolactinaemia.
- **MRI of the brain: the most accurate diagnostic test.** Be aware MRIs do not rule out small macroadenomas.

Levels of prolactin

- < 1000 → **drug-induced prolactinaemia**
- 1000 -- 3000 mU/l → **microprolactinoma**.
- > 3000 → **macroprolactinoma**.

Treatment of prolactinomas

Dopamine agonists (e.g. cabergoline, bromocriptine) are first-line treatment for prolactinomas, even if there are significant neurological complications

- **Dopamine agonist (DA) (Cabergoline and Bromocriptine)**
 - ⇒ **Dopamine agonists are first-line treatment for prolactinomas, even if there are significant neurological complications**
 - ⇒ they are able to normalize the prolactin levels, restore gonadal function and **reduce tumor size**
 - ⇒ **A meta-analysis suggested that cabergoline is more efficacious than bromocriptine in normalising prolactin and has a better side effect profile and is therefore the treatment of choice.**
 - ⇒ If patient is asymptomatic, there is no absolute requirement for treatment.
 - ⇒ **Side effects:**
 - Both pergolide and cabergoline may be associated with pericarditis, cardiac valve regurgitation, pericardial effusion and pulmonary hypertension.
 - **Ropinirole** may be an appropriate alternative in this case, otherwise **surgery** would be the next most appropriate step.
 - **Although cabergoline in higher doses used for Parkinson's disease can cause right-sided cardiac fibrosis, there is no evidence for this using the lower doses necessary for the control of PRL levels.**
 - ⇒ **Contraindications**
 - cardiac valve fibrosis
 - pulmonary fibrosis.
- **Pituitary surgery**
 - ⇒ rarely required in prolactinomas and is generally reserved for patients intolerant of or resistant to dopamine agonist therapy.
- **Radiotherapy** can be used to reduce the chance of tumour recurrence, but is rarely required.

Prolactinomas in pregnancy

- **Risk of pregnancy**
 - ⇒ The main concern for the mother is adenoma growth with potential mass effect and visual loss
 - ⇒ The risk of tumor enlargement during pregnancy is found to depend on tumor size:
 - 3% for microprolactinomas
 - 32% for macroprolactinomas that were not previously operated on
- **Before pregnancy:** For women with macroadenomas
 - ⇒ 1st line: dopamine agonist
 - ⇒ 2nd line (if size does not decrease) : transsphenoidal surgery
 - ⇒ pregnancy is not recommended in women with **drug resistant large macroprolactinomas** and they should not conceive even if the tumor is intrasellar, until the size is reduced by transsphenoidal surgery.

- During pregnancy

- ⇒ If possible, stop dopamine agonists as soon as the pregnancy is confirmed except in: invasive macroadenomas or pressure symptoms.
 - There is no evidence that DA is teratogenic, but Once pregnancy is established, DA is not necessarily required, and so most physicians recommend stopping it for the duration.
 - It is clearly not needed to treat hypogonadism and it is not needed to control size of adenoma as macroadenomas almost never spontaneously increase in size.
- ⇒ In case the patient becomes symptomatic with visual disturbance or progressive headaches, an MRI without gadolinium (not a CT) should be performed to assess changes in tumor size.
- ⇒ evidence of macroadenoma growth on MRI; performed for severe headaches or visual field abnormalities → cabergoline or bromocriptine
- ⇒ If treatment is required bromocriptine has the most safety data (the first drug of choice in symptomatic pregnant). Cabergoline may be considered if the adenoma does not respond to bromocriptine

- Breastfeeding

- ⇒ Asymptomatic: Breastfeeding is not contraindicated, but dopamine agonists should not be used, because they impair lactation.
- ⇒ woman who has visual field impairment: should not breastfeed and should be treated with a dopamine agonist

Cabergoline VS Bromocriptine

Comparison	Cabergoline	Bromocriptine
Dopamine receptors	D2 selectively	D2 and other dopamine receptors
	long acting (once or twice weekly → better tolerability and patient compliance)	Short acting (requires multiple doses per day)
Effectiveness in lowering the prolactin	More effective in lowering the prolactin	Less effective
Safety during pregnancy	Less data about safety	<i>Less teratogenicity than cabergoline</i>

Thyroid and parathyroid conditions

Physiological effects of thyroid hormones

Thyroid hormones production

- The thyroid utilises tyrosine and iodine to manufacture thyroxine and T3.
- Iodide is taken into the thyroid follicular cells by active transporters and then oxidised to iodine by thyroid peroxidase.
- Organification occurs when iodine is attached to tyrosine molecules which themselves are attached to thyroglobulin, forming monoiodotyrosine (MIT) and diiodotyrosine (DIT). The coupling of 2 molecules of DIT forms thyroxine.
- Maternal TRH readily crosses the placenta; maternal TSH and T4 do not.
- An enzyme called 5'-deiodinase in the blood removes an iodine molecule to convert T4 to the biologically active T3. So T4 can be considered a prohormone: it must be

- converted to T3 to exert any of its effects on the body. This conversion occurs throughout the body. In contrast, T4 can only be produced in the thyroid.
- Peripheral metabolism of thyroxine is the only source of T3.
 - Peripheral conversion is inhibited by glucocorticoids, β -blockers, and propylthiouracil(PTU)
 - T4 is much more abundant than T3 in the bloodstream. T3 is more biologically active than T4.
 - T3 has a much shorter half-life. T3 is more readily broken down by 5'-deiodinase.
 - The half-life of T3 is about one day (~ 20 hours), whereas the half-life of T4 is about one week (~ 190 hours). This longer half-life makes T4 suitable for use as a depot form that can be used replacement therapy.
 - Thyroid peroxidase first oxidizes iodide to iodine. Then, it attaches iodine to thyroglobulin. Then, it combines monoiiodotyrosine (MIT) and diiodotyrosine (DIT) or two molecules of DIT to make T3 and T4, respectively.
 - Excess iodide inhibits thyroid peroxidase. This is called the Wolff-Chaikoff effect.

Thyroid binding globulin (TBG)

- In the blood, more than 99% of T3 and T4 are bound to thyroid binding globulin (TBG) and thus not biologically active. The small unbound is called free T3 and T4. This is the biologically active form.
- TBG levels are increased during pregnancy and with oral contraceptive use because estrogen promotes liver TBG synthesis. In these patients, bound and total thyroid hormones are elevated while free T3 and T4 remain normal.

Causes of altered concentration of TBG

• ↑TBG	• ↓TBG
<ul style="list-style-type: none"> • Pregnancy • OCP and other sources of oestrogens • Tamoxifen • Hepatitis A; chronic active hepatitis • Biliary cirrhosis • Acute intermittent porphyria • Newborn state • Genetically determined 	<ul style="list-style-type: none"> • Androgens • Large doses of glucocorticoids • Cushing's syndrome • Chronic liver disease • Severe systemic illness • Active acromegaly • Nephrotic syndrome • Genetically determined • Drugs, e.g. phenytoin • Factitious thyrotoxicosis

Thyroid hormone receptors

- The thyroid hormone receptor is a nuclear receptor.
- The action of T3 requires entry into the nucleus, where the thyroid hormone receptors are found in cells throughout the body.
- The TRH receptor uses the Gq pathway, while the TSH receptor uses the Gs pathway.

Regulations

- TRH binds to a Gq receptor on anterior pituitary tissue → activate membrane-bound phospholipase C → ↑ inositol triphosphate (IP3) → ↑ intracellular calcium → activates protein kinase C → ↑ release of TSH.
- TSH binds to a Gs receptor on thyroid gland tissue → activate adenylate cyclase → promotes conversion of ATP to cAMP, which acts as a second messenger → ↑ synthesis and secretion of T3/T4.

Functions of thyroid hormones: 7 B's

- Brain maturation
- Bone growth (synergism with GH)
- β -adrenergic effects. $\beta 1$ receptors in heart CO, HR, SV, contractility; β -blockers alleviate adrenergic symptoms in thyrotoxicosis
- Basal metabolic rate (via Na⁺/K⁺ ATPase O₂ consumption, RR, body temperature)
- Blood sugar (glycogenolysis, gluconeogenesis) (**Enhance insulin sensitivity**)
- Break down lipids (lipolysis)
- Stimulates surfactant synthesis in **B**abies

What is the defect which is responsible for thyroid hormone dyshormonogenesis?

⇒ Defect in iodine organification

Thyrotropin is a glycoprotein hormone (glycosylated)

Calcitonin

Overview

- Polypeptide hormone
- **Produced by** the parafollicular cells (also known as C-cells) of the thyroid,

Calcitonin receptor

- found on **osteoclasts**, and in the kidney and regions of the brain,
- is a G protein-coupled receptor, which is coupled by G_s to adenylate cyclase and thereby to the generation of cAMP in target cells.
- It may also affect the ovaries in women and the testes in men.

Action

- ↓ bone resorption. Reduce blood calcium (Ca²⁺), opposing the effects of parathyroid hormone (PTH).
- **Calcitonin-gene related peptide causes vasodilatation.**
- Calcitonin lowers blood Ca²⁺ levels in two ways:
 1. **Major effect:** Inhibits osteoclast activity in bones
 2. **Minor effect:** Inhibits renal tubular cell reabsorption of Ca²⁺ and phosphate, allowing them to be excreted in the urine

Regulation

- Secretion of calcitonin is stimulated by:
 - ⇒ ↑ serum [Ca²⁺]
 - ⇒ gastrin and pentagastrin.

Calcitonin escape phenomenon

- **Despite high serum calcitonin levels, which mechanism best explains the normal calcium levels in a patient with thyroid nodule?**
 - ⇒ **High levels of calcitonin down regulates its receptor**
 - Calcitonin's primary function is to act on osteoclasts and decrease serum calcium levels.
 - Huge amounts of calcitonin are secreted in medullary carcinoma of the thyroid, or when calcitonin is used therapeutically to treat certain medical conditions, such as Paget's disease, osteoporosis, and hypercalcemia. Its effects on

osteoclasts disappear after one week of therapy. This is called the '**calcitonin escape phenomenon**'.

- The biochemical basis for the 'calcitonin escape phenomenon' is the down regulation of its receptor.
- Whenever the levels of calcitonin become high, they down regulate the receptor by rapid and prolonged down regulation of calcitonin receptor messenger RNA.

To remember that calcitonin keeps the calcium in the bones, think: Calci-bone-in!

Hypothyroidism

Epidemiology

- Affects around 1-2% of women in the UK
- Around 5-10 times more common in females than males.

Causes

- **Hashimoto's thyroiditis**
 - ⇒ Autoimmune disease, Associated with HLA-DR3
 - ⇒ **Most common cause**
 - ⇒ 10 times more common in women
 - ⇒ May cause transient thyrotoxicosis in the acute phase
 - **Early in the course of disease, T4 and TSH levels are normal and there are high levels of thyroid peroxidase antibodies** and, less commonly, anti-thyroglobulin antibodies.
 - **Thyroid radioiodine uptake may be increased** because of defective iodide organization, together with a gland that continues to trap iodine.
 - ⇒ **Associated with**
 - Other autoimmune diseases: IDDM, Addison's, pernicious anaemia, **coeliac disease**.
 - **Turner's syndrome, Down's syndrome**
 - **Thyroid lymphoma**
 - ⇒ **Features**
 - Features of hypothyroidism (eg hair loss, hoarse voice and periorbital oedema)
 - Goitre: firm, non-tender
 - Antibodies
 - ❖ anti-thyroid peroxidase (anti TPO) also known as (**Anti-microsomal antibodies**)
 - ❖ anti-thyroglobulin antibodies (anti-Tg)
- **Dietary iodine deficiency**
 - ⇒ **Common in parts of central Africa**, where the diet is poor in iodine and access to sea fish is relatively difficult. **Uncommon in the developed world**.
 - ⇒ Iodine daily requirement: according to WHO recommendations
 - Age >12 and adults → **150 microgram**
 - Pregnant and lactating women → 200 microgram
 - ⇒ It may present as goitre without hypothyroidism, or in severe cases can progress to frank hypothyroidism.
 - ⇒ **Urinary iodide excretion is the next investigation to establish the diagnosis**
 - As more than **95% of dietary iodide is excreted in urine**, a 24 hour urinary excretion of iodide is an excellent index of dietary iodine intake and can unmask an iodide deficiency state.

- **Postpartum thyroiditis (subacute lymphocytic thyroiditis)**
- **De Quervain's thyroiditis (subacute granulomatous thyroiditis)**
- **Riedel thyroiditis: a dense fibrosis that replaces normal thyroid parenchyma**
- **Iatrogenic:** after treatment of hyperthyroidism with anti-thyroid drugs, thyroidectomy or radioiodine.
- **Drug-induced**
 - ⇒ Amiodarone
 - ⇒ Lithium → goitre in up to 40% and **hypothyroidism** in about 20%.
- **Secondary (central) hypothyroidism (rare):**
 - ⇒ TSH is not appropriately elevated inspite of low T4.
 - ⇒ pituitary disorders → ↓ TSH levels → ↓ T3/T4 levels
- **Tertiary hypothyroidism:** hypothalamic disorders → ↓ TRH → ↓ TSH → ↓ T3/T4 levels

Hashimoto's thyroiditis = Hypothyroidism + Goitre + Anti-TPO

Hashimoto's thyroiditis is associated with thyroid lymphoma

Features

- **Symptoms related to decreased metabolic rate**
 - ⇒ Fatigue, decreased physical activity
 - ⇒ Cold intolerance
 - ⇒ Hair loss, brittle nails, and cold, dry skin
 - ⇒ Weight gain (despite poor appetite)
 - ⇒ Hypothyroid myopathy
 - ⇒ Woltman sign: a delayed relaxation of the deep tendon reflexes
 - ⇒ Entrapment syndromes (e.g., carpal tunnel syndrome)
- **Symptoms related to decreased sympathetic activity**
 - ⇒ Decreased sweating
 - ⇒ Cold skin (due to decreased blood flow)
 - ⇒ Constipation (due to decreased gastrointestinal motility)
 - ⇒ Bradycardia
- **Symptoms related to generalized myxedema**
 - ⇒ puffy appearance
 - ⇒ Myxedematous heart disease (dilated cardiomyopathy, bradycardia, dyspnea)
 - ⇒ Hoarse voice, difficulty articulating words
 - ⇒ Pretibial and periorbital edema: due to accumulation of glycosaminoglycans and hyaluronic acid within the reticular layer of the dermis. complex protein mucopolysaccharides bind water → nonpitting edema
- **Symptoms of hyperprolactinemia**
 - ⇒ Abnormal menstrual cycle; secondary amenorrhea; menorrhagia
 - ⇒ Galactorrhea
 - ⇒ Decreased libido, erectile dysfunction, delayed ejaculation, and infertility in men
- **Further symptoms**
 - ⇒ Impaired cognition; somnolence, depression

Investigations

- **Thyroid function tests**
 - ⇒ **TSH: Best initial screening test. Normal TSH levels generally rule out primary hypothyroidism and hyperthyroidism**
 - ⇒ FT4
- **Anti-TPO antibodies**
 - ⇒ present in 10% females without thyroid pathology

Associated laboratory manifestations

- **Euvolaemic hyponatraemia** often resulting from inappropriate production of antidiuretic hormone.
- Creatine kinase: increased in hypothyroid myopathy
- Macrocytic anemia
- **Glucose intolerance**
- **Dyslipidaemia**
 - ⇒ ↓thyroid hormones → ↓ use of glucose and FFAs as fuel → hyperlipidemia and glucose intolerance.
 - ⇒ The predominant lipid picture in hypothyroidism is **mixed dyslipidaemia** (↑LDL , ↑ triglycerides)
 - ⇒ **may well resolve following the appropriate replacement with thyroxine.**
 - ⇒ Hypothyroidism is a risk factor for statin induced myopathy, therefore before increase statin dose it is important to correct thyroid profile
- **Slightly raised bilirubin:** In hypothyroidism, the activity of bilirubin UDP-glucuronyl transferase is decreased, resulting in a reduction in bilirubin excretion.
- **Hyperprolactinemia → Hyperprolactin (hyperPRL) hypogonadism**
 - ⇒ Hypothyroidism → ↑↑TRH (thyrotropin-releasing factor) → act as prolactin-releasing factor → release of prolactin and hyperprolactinaemia.
- **Hypercarotenaemia (high blood levels of beta-carotene) → yellowing of the skin (xanthoderma).**
- **Clinically silent pericardial effusion is common in untreated hypothyroidism** (Pericardial or pleural effusions)

Anti-TPO antibodies are present in 10% females without thyroid pathology

Thyrotropin is a glycoprotein hormone (glycosylated)

**If the thyroid peroxidase (TPO) antibodies during early gestation are strongly positive.
What is the chance of developing hypothyroidism in the post-partum period? → 50%**

Management

- **Levothyroxine:** BNF recommends the **initial starting dose** as following:
 - ⇒ For patients with cardiac disease, or patients over 50 years: 25mcg od with dose slowly titrated.
 - ⇒ For other patients: 50-100mcg od
- **Follow-up:** following a change in thyroxine dose TFT should be checked after **8-12 weeks**
- **Target:** **TSH value 0.5-2.5 mU/l .**

If you made a diagnosis of Hashimoto's, what is the next best step in the management?

- **Rule out Addison's, short synacthen test** even if the sodium is normal. Addison's may coexist with Hashimoto's, masked by the hypothyroid. Treating hypothyroid will unmask the Addison's and precipitate adrenal crisis.

Monitoring

Monitoring of thyroid status

Thyroid-stimulating hormone (TSH) is the most sensitive indicator of thyroid status.

- Normal TSH result **suggests** → adequate thyroxin replacement & euthyroidism
- ↑↑ (TSH) with normal (T4) **suggest** → poor compliance
- ↓↓ (TSH) with normal - high (T4) **suggests** → over-replacement

Causes of persistently elevated TSH levels despite adequate thyroxine therapy:

- **Compliance (the commonest cause)**
- Drugs interaction such as:
 - ⇒ **rifampicin**
 - ⇒ calcium supplements (e.g. calcium carbonate)
 - ⇒ Amiodarone
 - ⇒ **ferrous sulphate** (give at least 2 hours apart)
 - ⇒ Omeprazole,
 - ⇒ Hormone replacement therapy (HRT) → ↑ thyroid binding proteins → ↓ free thyroid hormone → requiring an increase in thyroxine dose.
 - ⇒ Treatment with estrogens may necessitate a dose increase.
 - ⇒ Glucocorticoids interfere with thyroid hormone metabolism and the dose of levothyroxine may need to be reduced.
- Malabsorption syndromes like coeliac disease
- Nephrotic syndrome

Iron reduces the absorption of thyroxine

Complications

- **Myxedema coma**
 - ⇒ **Definition:** potentially life-threatening decompensation. usually occurs in the elderly who are typically non-compliant.
 - ⇒ **Features :** impaired mental status; hypothermia; bradycardia, myxedema
 - ⇒ **Treatment:**
 - Intravenous thyroid hormones : levothyroxine ; PLUS liothyronine
 - Treatment with **hydrocortisone** is recommended until Addison's disease can be excluded, as just **giving thyroid hormone alone may precipitate an adrenal crisis.**
 - rewarming.
- **Primary thyroid lymphoma**
 - ⇒ Hashimoto thyroiditis is the most common cause of hypothyroidism and the only known risk factor for primary thyroid lymphoma.
 - ⇒ Almost all primary thyroid lymphomas are non-Hodgkin large B-cell lymphomas.
- **Hashimoto's encephalopathy**
 - ⇒ Extremely rare
 - ⇒ Considered to be part of an autoimmune encephalitis.
 - ⇒ Often, the condition presents prior to the development of hypothyroidism and patients can be entirely euthyroid yet with quite profound neurological dysfunction.
 - ⇒ **Result in altered mental state, myoclonus and ataxia.**
 - ⇒ Should be suspected in TSH derangement however there may be no clinical evidence of thyroid dysfunction.
 - ⇒ **The next laboratory tests should be → Anti-thyroid peroxidase antibodies**
 - ⇒ It is a steroid responsive encephalopathy

A history of an acutely painful, left-sided goitre in euthyroid and apyrexial patient with normal labs and no prior history of thyroid disease ?

- **Haemorrhage into a cyst**

Pendred's syndrome

signs of deafness and hypothyroidism → Pendred's syndrome

Definition

- Pendred syndrome is an autosomal recessive disorder that results in the reduced activity of pendrin.
- Pendrin is important for:
 - ⇒ Iodide transport in the thyroid gland: defect → hypothyroidism with goiter.
 - ⇒ Electrolyte homeostasis in the inner ear: defect → sensorineural hearing loss
 - ⇒ Maintain sodium chloride balance in the distal nephron: defect → if treated with a thiazide diuretic that inhibits NCC, severe hypovolemia and metabolic alkalosis develop.

Features

- Hypothyroidism with goiter
- **Sensorineural deafness**
- Hypovolemia and metabolic alkalosis in response to thiazide diuretics.

Diagnosis

- **genetic testing** (Pendred's syndrome (**PDS**) gene, **chromosome 7**), (SLC26A4)
- audiometry and MRI imaging to look for **characteristic one and a half turns in the cochlea**, compared to the normal two and a half turns.

Treatment

- thyroid hormone replacement
- cochlear implants.

Riedel's thyroiditis

Definition

- A chronic autoinflammatory disease, characterized by conversion of regular thyroid parenchyma to diffuse fibrous growth that **may extend into the surrounding tissue**.

Features

- Typically presents as a painless, hard, solid thyroid enlargement (described as stony or woody.)
- Extension beyond the thyroid differentiates this from the fibrosing variant of Hashimoto thyroiditis.
- Associated hypothyroidism (although most patients are euthyroid), absence of cervical adenopathy and slow course are differentiate this from anaplastic thyroid cancer.
- Complications → Fibrotic invasion of adjacent anatomic structures (e.g. **Hypoparathyroidism**)

Diagnosis

- **Open surgical biopsy** is essential for the correct diagnosis.
- IgG4 levels are elevated in over 95% of cases.

Treatment

- **Steroids** and **tamoxifen** to inhibit connective tissue proliferation.
- **wedge resection of the thyroid isthmus** to alleviate tracheal obstruction is still the preferred surgical therapy.

Sick euthyroid syndrome

Definition

- A decrease in thyroid hormone levels that occurs in severe illness despite normal thyroid gland function.
- Now referred to as non-thyroidal illness.

Pathology

- **Increase in 5¹ deiodinase Type 3 levels**

Causes

- Any severe illness disease or organ failure
- **Common in intensive care patients**

Feature

- Low T4 and T3.
- TSH are typically low, but may be low-normal or normal.

Management

- Changes are reversible upon recovery from the systemic illness.
- **the most appropriate next step in management** → **repeat thyroid function tests in 3 months**

Subclinical hypothyroidism

Subclinical hypothyroidism in a patient younger than 70:

- **TSH > 10mU/l** → **Start levothyroxine replacement**
- **TSH 4-10mU/l** → **repeat the test in six months.**

Diagnosis

- TSH levels above the range but with normal levels of thyroxine (T4) and triiodothyronine (T3).

Epidemiology

- found in 8–10% of the population,
- more common in young women and increases with age.

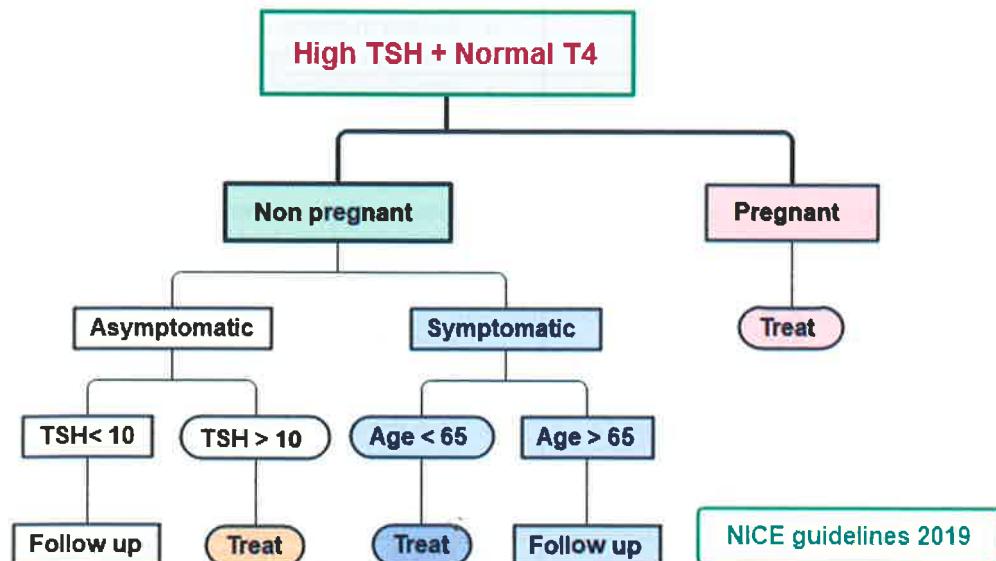
Significance

- may be associated with an increased risk of cardiovascular disease

- **Adverse pregnancy outcome:** ↑ risk of severe preeclampsia, placental abruption, preterm birth
 - ⇒ subclinical hypothyroidism with positive anti-thyroid peroxidase (TPO) antibodies tend to have the highest risk of adverse pregnancy outcomes

Indications for treatment

- **TSH > 10**
- Hypothyroid symptoms (regardless TSH level)
- Pregnancy or pregnancy planned in the near future



Management

- **TSH is between 4 - 10mU/L** (on 2 separate occasions 3 months apart).
 - ⇒ If symptomatic
 - < 65 years:
 - ❖ give a 6-month trial of levothyroxine
 - ❖ If there is no improvement in symptoms, stop levothyroxine
 - In older people (especially > 80 years) → follow a 'watch and wait' strategy, generally avoiding hormonal treatment'
 - ⇒ If asymptomatic → observe and repeat thyroid function in 6 months
- **TSH is > 10mU/L** (on 2 separate occasions 3 months apart) → start treatment (even if asymptomatic)

Monitoring

- Monitoring untreated subclinical hypothyroidism and monitoring after stopping treatment
 - ⇒ With features suggesting underlying thyroid disease, such as previous thyroid surgery or raised levels of thyroid autoantibodies → once a year
 - ⇒ Without features suggesting underlying thyroid disease → once every 2 to 3 years.

Abnormal thyroid function

Abnormal thyroid function tests

Test	Possible cause
High TSH + low free T4	Primary hypothyroidism
Low TSH + elevated free T4 and free T3	Primary hyperthyroidism
Low or normal TSH + low T4	Secondary hypothyroidism
Low TSH and normal free T4	T3 toxicosis (approximately 5% of thyrotoxicosis)
Low TSH and normal free T4 and free T3	<ul style="list-style-type: none"> • Subclinical hyperthyroidism • Recovery from thyrotoxicosis • Excess thyroxine replacement • Non-thyroidal illness
High TSH and high free T4 and free T3	<ul style="list-style-type: none"> • TSH-secreting pituitary tumour (2ry hyperthyroidism) • Thyroid hormone resistance • Heterophile antibodies, leading to spurious measurements of free T4 and free T3 • Thyroxine replacement therapy (including poor compliance)
High TSH and Normal free T4	<ul style="list-style-type: none"> • Poor compliance with thyroxine • Subclinical hypothyroidism
High free T4 and low normal free T3, normal TSH	<ul style="list-style-type: none"> • Amiodarone
Low or normal TSH and low normal free T4 and free T3	<ul style="list-style-type: none"> • Non-thyroidal illness • Central hypothyroidism • Isolated TSH deficiency
Normal TSH and low free T4	<ul style="list-style-type: none"> • Steroid therapy
Low TSH and low free T4	<ul style="list-style-type: none"> • Sick euthyroid syndrome (non-thyroidal illness)

Post-partum thyroiditis

Definition

- thyroid dysfunction occurring **within the first 6 months after delivery**.

Course of disease

- Hyperthyroid status followed by a hypothyroid phase at three to six months, followed by spontaneous recovery in one third of cases. In the remaining two-thirds, a single-phase pattern or the reverse occurs.

Features

- characteristic sequence of three phases: hyperthyroidism, followed by hypothyroidism, and then recovery

Pathophysiology

- The exact aetiology is unknown but **lymphocytic infiltration of the thyroid is typical**, suggesting auto-immunity.

Prevalence

- occurs in approximately 5-7% of females

Risk factors

- Common in whom thyroid peroxidase (TPO) antibodies were positive prior to delivery
- twice common in patients with type 1 diabetes mellitus.

Investigations

- **Thyroid peroxidase (TPO) antibodies** are found in 90% of patients

Management

- the thyrotoxic phase is not usually treated with anti-thyroid drugs as the thyroid is not overactive.
 - ⇒ Symptomatic treatment using → **beta-blockers** for relief of tremor or anxiety.
 - **Propranolol is typically used for symptom control**
- the hypothyroid phase is usually treated with **thyroxine**
 - ⇒ **withdrawal period after 6 months** to measure recovery of thyroid function.
 - ⇒ Stop thyroxine and reassess thyroid function in approximately one month.

Prognosis

- Recurrence of thyroiditis is common in subsequent pregnancies
- in up to 40% permanent hypothyroidism develops.

Subacute (De Quervain's) thyroiditis

Thyrotoxicosis with tender goitre = Subacute thyroiditis (De Quervain's thyroiditis)

Basics

- Subacute thyroiditis also known as De Quervain's thyroiditis and subacute **granulomatous** thyroiditis
- **It is associated with HLA-B35**

Pathophysiology

- Occur after viral infection
- thyroid inflammation drives increased release of stored thyroid hormone, rather than the clinical picture being due to overproduction of T3 and T4.

Features

Tender goitre, hyperthyroidism and raised ESR + globally reduced uptake on technetium thyroid scan is typical (De Quervian)

- typically presents with hyperthyroidism symptoms
 - ⇒ triphasic course of transient thyrotoxicosis, followed by hypothyroidism, followed by a return to euthyroidism.
 - ⇒ The thyrotoxic phase is due to thyroid follicular damage and release of preformed hormone
- painful goitre,
 - ⇒ The thyroid enlargement is typically rapid, occurring over a period of days.
 - ⇒ The thyroid gland will be **firm, enlarged bilaterally or unilaterally due to extravasation of colloid from the follicles causing a granulomatous reaction.**
- raised temperature (e.g. flu-like symptoms)

Investigations

- Hyperthyroidism
 - ⇒ As the condition resolves patients become hypothyroid and then euthyroid.
- raised ESR (>50 and usually 100), elevated CRP.
- Thyroid ultrasound: shows
 - ⇒ areas of hypoechoic echotexture
 - ⇒ decreased or normal vascular flow by Doppler.

- thyroid scintigraphy: **globally reduced uptake on iodine-131 scan**
 - ⇒ **the most helpful investigation in establishing the diagnosis → Radioactive iodine uptake scan**
 - ⇒ Radioiodine uptake is typically less than 1% at 24 hours (Tc 99m uptake is similarly low).

Management

- usually **self-limiting** - most patients do not require treatment
- symptomatic control.**
 - ⇒ Symptoms of hyperthyroidism:
 - should be managed with beta blockade as required,
 - no role for thionamides.
 - ⇒ thyroid pain may respond to aspirin or other NSAIDs
- steroids (Prednisolone)**
 - ⇒ in more severe cases, particularly if hypothyroidism develops

Prognosis

- The hypothyroidism is usually mild but persists for 2 - 4 months.
- return to normal thyroid function in >90% of patients
- A few patients (~5%) remain hypothyroid and need long-term thyroid hormone replacement.
- Recurrences are uncommon.

In De Quervain's thyroiditis, treatment is aimed at reducing inflammation with **NSAIDS** or **steroids in severe cases** (e.g. prednisolone 20–40 mg/day for two weeks and titrated down).

Subclinical hyperthyroidism

Patient with subclinical hyperthyroidism with measurable TSH and no features of exogenous thyroid dysfunction can be managed conservatively

Subclinical hyperthyroidism: normal FT4 and FT3 with a suppressed TSH level with non-specific symptoms

T3 levels should be performed where tests show normal T4 with suppressed TSH

Definition

- normal serum free thyroxine and triiodothyronine levels
- with a thyroid stimulating hormone (TSH) below normal range (usually < 0.1 mU/l)

Causes

- usually occurs in the setting of thyroid overactivity due to Graves' disease or autonomously functioning thyroid nodules sufficient to suppress pituitary TSH secretion but insufficient to cause an elevation of circulating hormones.
- multinodular goitre, particularly in elderly females
- excessive thyroxine may give a similar biochemical picture

Complications

- Cardiovascular (atrial fibrillation)
- Bone metabolism (osteoporosis)**
- impact on quality of life
- increase the likelihood of dementia

Management

- Observation
 - ⇒ **Repeat measurement of TSH (with serum FT4 and FT3)**
 - ⇒ TSH levels often revert to normal - therefore levels must be **persistently** low to warrant intervention
- therapeutic trial of low-dose antithyroid agents for approximately 6 months in an effort to induce a remission
- **Indication for definitive therapy:**
 - ⇒ presence of an unmeasurable TSH (sustained TSH suppression ($<0.1 \text{ mU/l}$)) **and/or**
 - ⇒ exogenous thyroid dysfunction
 - symptoms of hyperthyroidism,
 - **osteoporosis**
 - ❖ a DEXA scan is appropriate next line management to quantify the osteoporosis risk and inform the decision as to whether or not to treat the sub-clinical hyperthyroidism.
 - atrial fibrillation, or
 - unexplained weight loss
 - ⇒ The American Association of Clinical Endocrinologists recommends that treatment is considered in patients with a **persistently low TSH** level if they are **older than 65 years** or are **at risk of osteoporosis or heart disease**.

Prognosis

- Progression to overt hyperthyroidism occurs in 1-3 % of elderly patients per year.

Thyrotoxicosis

The PTH level in primary hyperparathyroidism may be normal

Causes

- Graves' disease (50-60% of cases of thyrotoxicosis)
- Toxic nodular goitre
- Toxic adenoma (Plummer's disease)
- Thyroiditis
 - ⇒ Subacute granulomatous thyroiditis (de Quervain thyroiditis)
 - ⇒ Subacute lymphocytic thyroiditis (e.g., postpartum thyroiditis)
- **Acute phase of Hashimoto's thyroiditis** (Hashitoxicosis): later results in hypothyroidism.
 1. Transient thyrotoxicosis in patients with early Hashimoto's disease resulting from the initial destruction of the thyroid gland and subsequent release of thyroid hormones.
 2. **Positive thyroid peroxidase antibodies and negative TSH receptor antibody**
- Amiodarone therapy
- β -hCG-mediated hyperthyroidism (hydatidiform mole, choriocarcinoma)
- **Secondary thyrotoxicosis : thyrotoxic with an abnormally 'normal' TSH.**
 - ⇒ TSH-producing pituitary adenoma
 - ⇒ **Ectopic TSH (e.g. struma ovarii, ovarian teratomas can produce exogenous TSH** causes secondary hyperthyroidism. can be visualized with a pelvic ultrasound or abdominal CT.)
 - **Negative neck ultrasound and neck exam in the setting of hyperthyroidism** and low radioiodine uptake.

- **Factitious hyperthyroidism:** Exogenous thyrotoxicosis, diagnosed by:
 - ⇒ **Undetectable thyroglobulin** (a precursor of thyroid hormones, indicates an external source of thyroid hormone)
 - ⇒ **Radioactive uptake thyroid scan**
 - endogenous causes of thyrotoxicosis → increased radioactive uptake
 - In thyrotoxicosis factitia, uptake is globally reduced.
- **T3 thyrotoxicosis**
 - ⇒ associated with 5% of cases of thyrotoxicosis.
 - ⇒ suppressed TSH, **low or normal** T4 and fT4, **high fT3**
- **Excess iodine ingestion**
 - ⇒ **Kelp is a very rich source of iodine.** Treatment is withdrawal of the kelp with monitoring of thyroid function.

Iodine excess

- **Jod-Basedow phenomenon:**
 - ⇒ **Hyperthyroidism following iodine excess** (e.g., after IV contrast administration, due to intake of amiodarone or other iodine-containing drugs, etc.)
 - ⇒ Mechanism: occurs due to either overactivation of the entire thyroid gland **or**, more commonly, autonomous nodules within the gland after iodine repletion without adequate feedback control from the pituitary gland.
- **Wolff-Chaikoff effect**
 - ⇒ **Hypothyroidism following iodine excess** (opposite effect to Jod-Basedow phenomenon)
 - ⇒ Mechanism: excess iodine inhibits thyroid peroxidase → decreases T3/T4 production

Thyrotoxicosis factitia (thyroxin abuse): The combination of **low thyroglobulin, decreased uptake on scintigraphy** and **raised T4**

T3 thyrotoxicosis should always be considered in patients with **suppressed TSH** and **normal T4 levels**, especially when patients are symptomatic.

Feature

- **General**
 - ⇒ **Heat intolerance**
 - ⇒ Excessive sweating because of increased cutaneous blood flow
 - ⇒ **Weight loss** despite increased appetite
 - ⇒ Frequent bowel movements (because of intestinal hypermotility)
 - ⇒ Weakness, fatigue
 - ⇒ Onycholysis: a separation of the nail from the nail bed.
 - ⇒ Infiltrative dermopathy, especially in the pretibial area (**pretibial myxedema**)
- **Goiter:** Diffuse, smooth, nontender goiter; often audible bruit
- **Eyes**
 - ⇒ Lid lag: caused by adrenergic overactivity, which results in spasming of the smooth muscle of the levator palpebrae superioris
 - ⇒ Lid retraction: "staring look"
 - ⇒ **Lid retraction and lag are signs of sympathetic overactivity, and occur in any thyrotoxic state** (thyroxine potentiates the action of catecholamines).
 - ⇒ Graves ophthalmopathy (exophthalmos, edema of the periorbital tissue)

- **Decreased libido**
- **Cardiovascular**
 - ⇒ Palpitations, tachycardia , irregular pulse (due to atrial fibrillation/ectopic beats)
 - caused by increased beta-adrenergic tone.
 - Atrial fibrillation (AF) occurs in 10% to 25% of patients with hyperthyroidism
 - ⇒ Hypertension with widened pulse pressure
 - Systolic pressure is increased due to increased heart rate and cardiac output.
 - Diastolic pressure is decreased due to decreased peripheral vascular resistance.
- Endocrinological
 - ⇒ Female: oligo/amenorrhoea, anovulatory infertility, dysfunctional uterine bleeding
 - ⇒ Male: gynecomastia, decreased libido, infertility, erectile dysfunction
- Musculoskeletal
 - ⇒ **Fine tremor** of the outstretched fingers
 - ⇒ Hyperthyroid myopathy: Typically affects proximal muscles (e.g., hip flexors, quadriceps) more than distal muscles. Serum creatine kinase levels are most often normal
 - ⇒ Osteopathy: osteoporosis due to the direct effect of T3 on osteoclastic bone resorption
- Neuropsychiatric
 - ⇒ Anxiety, Restlessness, Insomnia
 - ⇒ Hyperreflexia

Investigations

- **Thyroid function tests: low TSH, plus high T4 and T3.**
 - ⇒ The most sensitive test to diagnosis hyperthyroidism is **TSH level (initial screening test)**.
 - ⇒ In primary hyperthyroidism the TSH should always be suppressed by negative feedback
 - ⇒ **Non-suppressed (TSH)** suggests → excessive TSH production by the pituitary gland → the possibility of a thyrotroph adenoma → do **MRI scan pituitary gland**
 - ⇒ **T3 is more sensitive** because occasional cases of isolated T3 toxicosis can occur.
- **TSH receptor antibody (TRAb): for suspected Graves disease** without characteristic features
- **Thyroid ultrasound with Doppler**
 - ⇒ first-line for pregnant/lactating patients, palpable nodules or suspected thyroiditis
 - ⇒ Increased perfusion: either diffuse (Graves' disease, toxic adenoma) or nodular (toxic MNG)
 - ⇒ Decreased perfusion: destructive causes of hyperthyroidism (e.g., subacute thyroiditis or postpartum destructive thyroiditis)
- **Thyroid scintigraphy:** Radioactive iodine uptake measurement (RAIU test)
 - ⇒ **first-line for most patients with uncertain diagnoses**, e.g., suspected thyroid adenoma or toxic MNG
 - ⇒ Assess functional status of thyroid nodules
 - Hot nodule: Hyperfunctioning tissue takes up large amounts of radioactive iodine
 - Cold nodule: Non-functioning nodules do not take up any radioactive iodine and appear "cold", but the surrounding normal thyroid tissue takes up radioactive iodine and appears "warm"
 - ⇒ Identify ectopic thyroid tissue
 - ⇒ Contraindications: pregnant or breastfeeding women

- General laboratory findings
 - ⇒ Serum glucose levels typically **increase** in patients with hyperthyroidism.
 - ⇒ **Hypocholesterolemia** due to increased LDL receptor expression.
 - ⇒ Serum cholesterol: decreased total cholesterol, LDL, and HDL
 - ⇒ **CBC in thyrotoxic Graves' disease is most likely to show:**
 - **Mild leukopenia with relative lymphocytosis** (mild neutropenia and lymphocytosis)
 - Normochromic anaemia
 - Rarely, thrombocytopenia.
 - ⇒ High bone turnover and **osteoporosis** may be associated with thyrotoxicosis. Bone turnover involves increased osteoclastic and osteoblastic activity, leading to **elevated alkaline phosphatase levels** derived from bone.
 - ⇒ **Increased** levels of sex hormone-binding globulin (**SHBG**)

Which blood tests is most sensitive in establishing whether there is excess thyroid activity?

- Free T3 level

Management

- Treatment of hyperadrenergic symptoms: beta blockers (first line)
 - ⇒ Propranolol is effective in controlling all symptoms prior to initiation of specific therapy (e.g. carbimazole, which will have a more delayed effect on symptoms).
 - ⇒ If there are contraindications to beta blockers, e.g., severe asthma, Raynaud phenomenon, consider CCBs: verapamil OR diltiazem
- Antithyroid drugs (ATDs)
 - ⇒ Most patients: methimazole
 - ⇒ Thyroid storm or first trimester of pregnancy: propylthiouracil
 - ⇒ Duration of therapy for Graves' disease: typically 12–18 months
 - ⇒ Contraindications to ATDs, e.g., liver disease
- Radioactive iodine ablation (RAIA)
 - ⇒ destruction of thyroid tissue via radioactive iodine (iodine-131)
 - ⇒ Indicated for Toxic MNG, toxic adenoma and failure of antithyroid drugs (ATDs) in Graves disease.
 - ⇒ Contraindicated in pregnant/breastfeeding women and moderate to severe Graves ophthalmopathy.
- Thyroid surgery
 - ⇒ The efficacy of antithyroid drugs and RAIA has reduced the need for thyroid surgery.
 - ⇒ Indications: Large goiters (≥ 80 g) or obstructive symptoms, suspected thyroid malignancy and Graves ophthalmopathy.

Secondary thyrotoxicosis:

- **Thyrotoxic with an abnormally 'normal' TSH.**
- Pituitary adenoma
- Prior to pituitary surgery → restoration of euthyroidism with **somatostatin analogues**.

In acute thyrotoxicosis, stop aspirin as it can worsen the storm by displacing T4 from thyroid binding globulin

Thyrotoxicosis is associated with reversible cardiomyopathy

Management of thyrotoxicosis in pregnancy

Suspect a molar pregnancy or choriocarcinoma if severe hyperthyroidism manifests during pregnancy

Transient thyrotoxicosis and/or hyperemesis gravidarum

- Supportive therapy
- Management of dehydration, and hospitalization if needed.
- Anti-thyroid drugs (ATDs) are not recommended, though β -blockers may be considered.

- Early pregnancy (1st trimester) → Propylthiouracil (PTU)
 - ⇒ Due to the small risk of fetal abnormalities with carbimazole it is recommended to use PTU in the first trimester during organogenesis and then carbimazole in trimester 2 + 3.
 - ⇒ Propylthiouracil (PTU) is highly protein bound making it less likely to cross the placenta or breast milk.
 - ⇒ Carbimazole has rarely been associated with aplasia cutis of the neonate
- Late pregnancy (2nd + 3rd trimester) → Carbimazole
 - ⇒ Propylthiouracil associated with hepatotoxicity
 - ⇒ Despite this the BNF states both drugs may be used in pregnancy.
- Postpartum Patients
 - ⇒ Carbimazole is recommended by European Thyroid Association Guideline during lactation, given the concerns about PTU-mediated hepatotoxicity.
- Contraindications
 - ⇒ Block-and-replace regimes should not be used in pregnancy
 - ⇒ Radioiodine therapy is contraindicated
- Monitoring and targets
 - ⇒ Maternal free thyroxine levels should be kept in the upper third of the normal reference range to avoid fetal hypothyroidism
 - ⇒ In women being treated with anti-thyroid drugs (ATDs) in pregnancy, FT4/TT4 and TSH should be monitored approximately every 4 weeks.
- Thyroid-stimulating hormone receptor antibodies
 - ⇒ In a patient with a past medical history of Graves' disease who is clinically and biochemically euthyroid who is planning pregnancy: check thyroid-stimulating hormone receptor antibodies (as it can cross the placenta and cause foetal problems.): If they are positive, then treatment should be initiated to control the antibody levels, despite the normal TSH and T4.

Due to the small risk of fetal abnormalities with carbimazole it is recommended to use PTU in the first trimester during organogenesis and then carbimazole in trimester 2 + 3.

A 10 weeks pregnant C/O anxiety and an inability to sleep. Blood results show: total thyroxine (T₄) 160 nmol/l (normal range 70–140 nmol/l), free T₄ 27 pmol/l (9–25 pmol/l) and thyroid-stimulating hormone (TSH) 0.2 mU/l. Which management of choice in this patient?

- Observe and repeat thyroid function tests in one month
- Diagnosis: Physiological hyperthyroidism

Hyperthyroidism with non-suppressed TSH

- Elevated free T4 and free T3 + non-suppressed TSH (normal or elevated) = think of either :
 - ⇒ TSH-secreting pituitary tumour OR
 - ⇒ Thyroid hormone resistance
- TSH-secreting adenoma
 - ⇒ ↑Alpha subunit: the next investigation to differentiate it from thyroid hormone resistance. elevated alphaSU: TSH ratio (usually 1:1). A molar ratio of Alpha - subunit to TSH of > 5.7 is considered diagnostic.
 - ⇒ Pituitary MRI should be done to look for a pituitary mass.
 - ⇒ Treatment: Trans-sphenoidal resection of the tumour is the therapy of choice.
- Thyroid hormone resistance
 - ⇒ Mechanism: THB gene defects,
 - ⇒ Features: Usually clinically euthyroid with only goitre. Sometimes: goitre with short stature, hyperactivity, attention deficits, learning disability,
 - ⇒ Diagnosis: gene sequencing (sequencing the thyroid hormone receptor gene) can confirm diagnosis in 85%.
 - ⇒ Treatment: Most cases require no treatment. If needed, it is usually B-adrenergic blockers

MRCPUK-part-1-September 2007 exam: Pregnant lady investigated for excessive sweating and tremor. Blood tests reveal the following: TSH < 0.05 mU/l. T4 = 188 nmol/l. What is the most appropriate management? **Propylthiouracil**

Toxic multinodular goitre (TNG) (Plummer's disease)

Definition

- multiple autonomously functioning thyroid nodules that secrete excess thyroid hormones.

Epidemiology

- second most common cause of hyperthyroidism in the Western world, after Graves disease.
- most common cause of hyperthyroidism in elderly and in areas of endemic iodine deficiency.
- Develops in 10% of patients with a long-standing nodular goiter
- Sex: ♀ > ♂
- Age: often > 60 years

Pathophysiology

- Iodine deficiency → ↓ T4 → thyroid cell hyperplasia to compensate for the low levels of T4 → ↑thyroid cell replication → somatic mutations of the TSH receptor → further growth → clonal proliferation → multiple nodules.
- Somatic mutations of the TSH receptors and G α protein → activation of cyclic adenosine monophosphate (cAMP) cascade of the inositol phosphate pathways → functional autonomy of the thyroid
- Multiple somatic mutations of TSH receptor occur in long-standing goiters (> 60% of cases) → autonomous functioning of some nodules (toxic MNG) → hyperthyroidism (due to ↑ release of both T3 and T4)

Features

- goiter with multiple palpable nodules
- thyrotoxicosis

- **Pemberton sign** is the **obstruction of the thoracic inlet** by extending the arms over the head, and can be positive in cases of multinodular goiter.

Diagnosis

- Ultrasonography is a highly sensitive to detect nodules
- Thyroid scintigraphy → **patchy uptake**
 - ⇒ Increased radioiodine uptake by multiple hyperfunctioning (hot) nodules
 - ⇒ Decreased uptake (suppression) by the rest of the gland and intervening parenchyma
- CT of the chest → is the investigation of choice to determine the degree of retrosternal involvement
- Histopathology of resected tissue: patches of enlarged follicular cells distended with colloid and with flattened epithelium

Thyroid nuclear scintigraphy

- **Toxic nodular goiter (TNG)** → patchy uptake.
- **Graves' disease** → homogeneous diffuse uptake.
- **Thyroiditis** → low uptake.

Treatment

- **The treatment of choice is radioiodine therapy**
 - ⇒ Recurrence of multinodular goitre after RAI → **The next best step is a further dose of RAI** after 6 months of the first RAI therapy.
- **Surgical therapy is** usually reserved for young individuals, patients with 1 or more large nodules or with obstructive symptoms, patients with dominant nonfunctioning or suspicious nodules, patients who are pregnant, patients in whom radioiodine therapy has failed, or patients who require a rapid resolution of the thyrotoxic state.

Toxic thyroid adenoma (solitary toxic nodule)

Overview

- Typically, a **single large thyroid nodule** accompanied by clinical and biochemical **hyperthyroidism**.
- This nodule is **almost always benign**

Pathophysiology

- **Gain-of-function mutations of TSH receptor gene** in a single precursor cell → autonomous functioning of the follicular cells of a single nodule → **focal hyperplasia of thyroid follicular cells** → toxic adenoma
- The autonomous nodule overproduces thyroid hormones → hyperthyroidism → decrease in pituitary TSH secretion → **suppression of hormone production from the rest of the gland**

Diagnosis

- **Thyroid iodine uptake scan:**
 - ⇒ Hot area surrounded by extranodular thyroid tissue.
 - ⇒ **Thyroid tissue surrounding a toxic adenoma typically has suppressed function.**
- **In the absence of any thyroid auto-antibodies which argue against both Graves' disease and Hashitoxicosis, the most likely diagnosis is a solitary toxic nodule.**

Treatment

- **Initial treatment**
 - ⇒ Control symptoms with beta-blockers and thioamides until euthyroidism is achieved, followed by tapering of beta-blockers
- **Definitive treatment**
 - ⇒ Non-pregnant, non-lactating adult **with no mass effect**:
 - **1st line** → **Radioactive iodine therapy**
 - **2nd line** → subtotal thyroidectomy
 - ⇒ Non-pregnant, non-lactating adult **with mass effect**:
 - **1st line** → subtotal thyroidectomy
 - ⇒ Pregnant or lactating:
 - **1st line** → anti-thyroid drugs
 - **2nd line** → subtotal thyroidectomy

Graves' disease

Graves' disease is the most common cause of thyrotoxicosis

Overview

- Graves' disease is the most common cause of thyrotoxicosis.
- typically seen in women aged 30-50 years.
- **associated with the presence of HLA-DR3 and HLA-B8**
- 50% of patients with Graves disease have a family history of autoimmune disorders
- Triggers: Physical or psychological stress and pregnancy

Pathophysiology

- B and T cell-mediated autoimmunity → production of stimulating immunoglobulin G (IgG) against TSH-receptor (TRAb; type II hypersensitivity reaction) → ↑ thyroid function and growth → hyperthyroidism and diffuse goiter
- there are antibodies to the TSH receptor mimicking the action of endogenous TSH. Binding to the TSH receptor then activates adenyl cyclase and results in increased secretion of thyroid hormones (**Antibodies overstimulating adenyl cyclase**)

Features

- General features of thyrotoxicosis
- **Specific features seen in Graves' but not in other causes of thyrotoxicosis**
 - ⇒ Eye signs (**30% of patients**): **exophthalmos, ophthalmoplegia**
 - ⇒ **Pretibial myxedema** (commonly described as **orange peel skin present on both shins**) → pathognomonic
 - raised, indurated pinkish patches.
 - may appear years before, or after, hyperthyroidism.
 - ⇒ **Thyroid acropachy** (a dermopathy characterized by soft-tissue swelling of the hands and clubbing of the fingers). Radiographic imaging of affected extremities typically demonstrates periostitis, most commonly the metacarpal bones.
 - ⇒ Thyroid bruit: **presence of goitre is not necessary**, although usually there is a small palpable goitre.
 - ⇒ **Anti-TSH receptor stimulating antibodies (90%)** → **specific for Graves' disease**
 - ⇒ Globally increased uptake on thyroid scan.

The most likely associate of Graves' disease is vitiligo occurring in approximately 7% of cases.

Triad of Graves disease

1. Diffuse goiter (smooth, uniformly enlarged goiter)
2. Ophthalmopathy (Exophthalmos)
3. Dermopathy (pretibial myxedema): non-pitting edema and firm plaques on the anterior/lateral aspects of both legs

Management

- Treatment of hyperadrenergic symptoms → Beta blockers: first line: propranolol
- Anti-thyroid drugs (ATDs)
 - ⇒ ATD titration
 - carbimazole is started at 40mg and reduced gradually to maintain euthyroidism
 - typically continued for 12-18 months
 - fewer side-effects than those on a block-and-replace regime
 - **Long-term remission following antithyroid drugs is of the order of 15%, with the vast majority relapsing.** Thus, frequently, radio-iodine is advocated as a primary treatment - particularly for multi-nodular or toxic solitary nodules.
 - ⇒ Block-and-replace
 - carbimazole is started at 40mg
 - thyroxine is added when the patient is euthyroid
 - treatment typically lasts for 6-9 months
 - this approach is associated with 50% long term remission rate (**the relapse rate after treatment is 50%**)
- Radioiodine iodine (RAI) treatment: in refractory cases to medical management
- Surgery: less commonly used and usually reserved for patients with large goitre, compressive symptoms or intolerance to antithyroid drugs and difficulties in administering radioiodine

The principal test used to follow the immediate effect of treatment of hyperthyroidism is the serum free T4 concentration. Measurement of serum TSH can be misleading in the early follow-up period because it can remain low for weeks or even months, even when the patient is biochemically euthyroid or even hypothyroid,

Which factor can be used as a predictor of relapse of hyperthyroidism before pharmacologic treatment is discontinued?

Positive thyroid-stimulating autoantibody test. (This is a good predictor of relapse, but rates of relapse are still high when thyroid-stimulating autoantibodies disappear).

Pregnant woman with a history of **Grave's** disease should have **thyroid stimulating hormone binding antibody titres measured** even if euthyroid as the antibodies can cross the placental barrier

Antithyroid drugs

Agents

- Methimazole, Carbimazole, Propylthiouracil
- Methimazole is the active metabolite of carbimazole

Mechanism of action

- Inhibits thyroid hormone production via inhibition of thyroid peroxidase → blockade of iodide oxidation, organification, coupling (**Inhibition of the iodination of tyrosine**)
- Propylthiouracil also lowers peripheral conversion of T4 to T3 by inhibiting 5'-deiodinase.

Onset of action

- Slow onset of action (3–4 weeks)
- Methimazole has a faster onset of action and fewer side effects than propylthiouracil

Adverse effects

- Carbimazole-induced agranulocytosis** (the major complication)
 - defined as neutrophil count less than $0.5 \times 10^9/L$
 - the incidence of leukopenia/neutropenia with carbimazole is less than 1%.
 - should be stopped if neutrophil count below $1.5 \times 10^9/L$ (1.5-7).
 - In fact, a mild decrease in WBC can also occur with hyperthyroidism.
 - If neutrophil count are just below normal → The most appropriate treatment would be to continue the carbimazole.
 - Treatment
 - thionamides should be withdrawn
 - appropriate antibiotics (broad spectrum cephalosporin)
 - occasionally, granulocyte colony-stimulating factor (G-CSF) is required when white count fails to respond.
- Hepatotoxicity (seen with propylthiouracil use)**
- Teratogenicity:** increased risk of congenital malformations with carbimazole and methimazole (e.g., aplasia cutis)
 - Neonatal hypothyroidism will occur in approximately 10% of babies, because **carbimazole crosses the placenta** and switches off the fetal thyroid axis. The goitre that occurs is transient and will disappear following delivery
 - also, propylthiouracil cross the placenta but less freely than carbimazole, although thyroxine does not.
- Allergy/hypersensitivity
 - pruritic rash (particularly with methimazole)
 - ANCA-associated vasculitis (propylthiouracil)

As methimazole and carbimazole are teratogenic, propylthiouracil is recommended in the first trimester. After the first trimester, switch back to carbimazole or methimazole because of the hepatotoxic effects of propylthiouracil.

Interaction

- Carbimazole effect is potentiated by the liver enzyme-inhibitor (eg: erythromycin)

Carbimazole (CBZ) VS Propylthiouracil (PTU)

	Carbimazole (CBZ)	Propylthiouracil (PTU)
Action	↓thyroid peroxidase	↓thyroid peroxidase + ↓ ¹ deiodinase type 1 → ↓peripheral conversion of T ₄ to T ₃
Potency	More (15 times as potent as PTU)	Less

	Carbimazole (CBZ)	Propylthiouracil (PTU)
Structure	less protein bound, more transfer across placenta	more protein bound, less transfer across placenta
Teratogenicity	Associated with aplasia cutis	Less associated with aplasia cutis
Major side effects	Agranulocytosis	Hepatotoxicity
use in pregnancy	2nd and 3rd trimester	1st trimester

Radioactive iodine therapy (RAI)

Definition: destruction of thyroid tissue via radioactive iodine (iodine-131)

Indications

- Graves' disease refractory to medical management
- Toxic multinodular goitre

Preparation before RAI

- Anti-thyroid drugs is often used prior to RAI due to the risk of early deterioration of thyrotoxicosis. **This depletes the intrathyroidal stores of hormone to prevent re-exacerbation of thyrotoxicosis in the weeks following treatment due to release of preformed thyroid hormone.**
- **Carbimazole needs to be stopped at least 7 days prior to radioiodine to ensure appropriate uptake.**
- Avoid excess iodine for 7 days prior to RAI.

Procedure

- **Single** oral dose of iodine-131
- The recommended dose of RAI is typically between **500 - 800 MBq**

Advice post procedure

- Patients should be advised to keep babies, children under five, pregnant women and pets **at arm's length for two to three weeks**
- Females are advised to avoid pregnancy for at least **6 months** after radioactive iodine treatment
- Males are advised not to cause a pregnancy for **6 months** after radioactive iodine

Advantages

- **Goitre shrinkage** may occur in up to 30% following RAI.

Adverse effects

- **Thyrotoxic symptoms**
 - ⇒ Mild thyrotoxic symptoms after radioiodine occur in about one-third of patients,
 - ⇒ About 4% of patients develop a clinically significant **radiation-induced thyroiditis**. Should be treated symptomatically with **beta blockers**.
- **Hypothyroidism**
 - ⇒ Early post-radioiodine hypothyroidism might be transient.
 - ⇒ **Hypothyroidism is the most common adverse effect.**
 - ⇒ **Proportion of patients who become hypothyroid**
 - depends on the dose given, but as a rule the majority of patient will require thyroxine supplementation after 5 years

- approximately 80% will have long-term hypothyroidism following radio-iodine.
- Flare of Graves' eye disease (\uparrow thyroid eye disease in 15% of patients with Grave's disease)
 - \Rightarrow patients with thyroid eye disease should be treated with steroids for one to two weeks prior to starting radioiodine therapy.

Contraindications

- Pregnancy
- Breastfeeding
- Active thyroid eye disease (unless providing steroid cover)
- Radioiodine therapy should be avoided until 8 weeks following CT contrast administration. the iodine in the CT contrast medium competes with the radioactive iodine (I^{131}) for binding sites $\rightarrow \downarrow$ thyroid uptake of radioiodine.

Radioiodine therapy is the treatment of choice for patients with a relapse of Graves' disease in the absence of contraindications, such as pregnancy and active severe Graves ophthalmopathy

Thyroidectomy

Indications

- Large goiters (≥ 80 g) or obstructive symptoms
- thyroid malignancy
- Graves' disease with severe ophthalmopathy

Complications

- Transient hypoparathyroidism
 - \Rightarrow due to local trauma at the time of surgery
 - \Rightarrow occur in 8 – 10% of cases (the most likely post-operative complication)
 - \Rightarrow Rarely becomes permanent hypoparathyroidism in fewer than 1% of patients.
 - \Rightarrow Usually presents 24-48 hours postoperatively
- permanent hypoparathyroidism seen in 1-2%
- Infection is seen in 1-2%
- Bleeding is less common, seen in around 0.5% or less
- Permanent recurrent laryngeal nerve palsy occurs in 1% of patients;
 - \Rightarrow Recurrent laryngeal nerve injury leads to a hoarse voice, because of paralysis of the posterior cricoarytenoid muscle, which is responsible for opening the vocal cord.
 - \Rightarrow **superior laryngeal nerve palsy affects more patients (3-4% in case series).**

Which structures is most closely related to the recurrent laryngeal nerve?

- Inferior thyroid artery
- The superior thyroid artery runs closest to the superior laryngeal nerve.

Amiodarone and the thyroid gland

Overview

- Amiodarone, a class III antiarrhythmic drug can induce thyroid dysfunction (both hypo- and hyperthyroidism), which is due to amiodarone's high iodine content and its direct toxic effect on the thyroid. Amiodarone contains 75 mg of iodine per 200 mg tablet (40% iodine by weight).
- Around 1 in 6 patients taking amiodarone develop thyroid dysfunction
- Amiodarone has a wide tissue distribution, very long half-life (100 days), very lipophilic, and can result in prolonged effects even after stopping therapy for several months.

Amiodarone-induced hypothyroidism (AIH)

- **Epidemiology**
 - ⇒ Amiodarone-induced hypothyroidism is the commonest side effect associated with amiodarone treatment in iodine replete areas (in contrast to amiodarone induced thyrotoxicosis more commonly seen in iodine depleted areas).
- **Pathophysiology**
 - ⇒ High iodine content of amiodarone causing a Wolff-Chaikoff effect (an autoregulatory phenomenon where thyroxine formation is inhibited due to high levels of circulating iodide)
 - ⇒ Amiodarone **inhibits the peripheral conversion of T₄ to T₃** (normal T₄, ↓ T₃, ↑ TSH).
- **Management**
 - ⇒ Same as for primary hypothyroidism.
 - ⇒ Doses larger than normal, is often required
 - ⇒ Amiodarone should only be discontinued if it fails to control the underlying arrhythmia.

Amiodarone is most likely to cause a false increase in which of these laboratory values?

Free T₄. (Amiodarone can cause a reduced peripheral conversion of T₄ to T₃).

Amiodarone-induced thyrotoxicosis (AIT)

Amiodarone-induced thyrotoxicosis (AIT) may be divided into two types:

Differentiating between the two forms of Amiodarone-Induced Thyrotoxicosis (AIT)

	AIT type 1	AIT type 2
Epidemiology	Most often seen in iodine-deficient areas.	Most common in Europe and North America
Pathophysiology	Amiodarone contains ↑ iodine → ↑ thyroid hormone synthesis (Jod-Basedow effect)	↑ release of T4 and T3 due to a destructive thyroiditis
History	Occurs in patients with underlying thyroid pathology, such as a nodular goitre or Graves' disease.	Occurs in patients without underlying thyroid disease.
Goitre	Present	Absent
Color Doppler	↑ Blood flow	↓ Blood flow
Iodine-131 uptake scan	normal or high	Minimal or none
IL-6 levels	Low or normal	Markedly elevated
Management	Carbimazole	Corticosteroids ± Antithyroid

Differentiation between type 1 and type 2

- Colour flow Doppler is most likely test to differentiate between Amiodarone induced thyrotoxicosis (AIT) type 1 and type 2. It appears to be superior to IL-6 which may be markedly elevated in AIT type 2, however may also be raised by concurrent non-thyroidal illness.

AIT initial management

- Usually Type 1 AIT is treated with high doses of anti-thyroid drugs to block thyroid hormone synthesis. Type 2 thyrotoxicosis is treated with glucocorticoids.
- Due to practical difficulties to distinguish between the 2 types, often a combination of steroids and thionamides is the best first-line management used for treatment of AIT.
 - ⇒ A rapid response suggests type 2 AIT; thionamides can be tapered.
 - ⇒ A poor initial response suggests type 1 AIT; the steroids can be tapered, and the patient can be treated for type 1 AIT.

Withdrawal of the amiodarone in AIH & AIT

- For AIH: continue amiodarone, treat with thyroid hormone. Amiodarone should only be discontinued if it fails to control the underlying arrhythmia.
- For type I AIT:
 - ⇒ Amiodarone should not be discontinued until hyperthyroid symptoms are well controlled with thionamides, since worsening hyperthyroid symptoms due to increased T3 levels may occur when the amiodarone is discontinued.
- For type 2 AIT:
 - ⇒ Amiodarone should be stopped, if possible (if the patient does not have a life-threatening arrhythmia that requires amiodarone therapy. In cases such as VT, this decision should be considered carefully in conjunction with a cardiologist, so the next management step will be Start carbimazole 40 mg od.)
 - ⇒ Discontinuation of the drug has no immediate benefit. Even if amiodarone is stopped, thyrotoxicosis persists for up to 8 months because of the drug's long half-life.

The presence of markedly **elevated serum IL-6** and low thyroidal radioiodine uptake in a patients without underlying thyroid disease suggests the presence of **amiodarone-induced thyroiditis** as the etiology of thyrotoxicosis.

Thyroid eye disease

Feature	Assessment	Frequency
Lid lag / lid retracted	Measure lid fissure width	50-60%
Grittiness, discomfort, periorbital oedema, pain, excessive tears.	Self-assessment score by patient	40%
Proptosis (aka exophthalmos) this is where the eye bulges out of its socket.	Exophthalmometry or evaluation on MR/CT scan.	20%
Extraocular muscle dysfunction –typically causes diplopia (double vision) when looking up and out.	Hess chart + CT/MR to detect muscle size	10%
Corneal involvement, causing exposure keratitis	Fluorescin staining	<5%
Loss of sight due to optic nerve compression	Visual acuity tests, visual field tests. CT/MR scan	<1%

Overview

- Also called Graves' Ophthalmopathy or Graves' eye disease
- Graves' eye disease can occur in euthyroid, hypothyroid or hyperthyroid setting.**
- Thyroid eye disease affects between 25-50% of patients with Graves' disease.**
- In about 10% of patients, the signs will only be unilateral.**
- Ophthalmopathy **may occur before the onset of hyperthyroidism**, or as late as 20 years afterward.
- Risk factors** for the development of Graves' orbitopathy include genetics, female sex, smoking, and prior radioiodine therapy.

Graves' eye disease can occur in euthyroid, hypothyroid or hyperthyroid setting.

Definitions

- Exophthalmos** (also known as **proptosis**) is the protrusion of one eye or both anteriorly out of the orbit.
- Lid retraction:** When looking at the patient from the side, you see that the eyes are proptosed.
- Lid lag:** When the patient follows your finger, moving downwards from above, the sclera can temporarily be seen above the iris.

Pathophysiology

- TSH autoantibodies are present in the orbital cavity; bind TSH receptor antigen (**autoimmune reaction**) on cells; **lymphocytic infiltration into the orbital tissues** → inflammation and release of cytokines from CD4+ T cells → stimulates fibroblasts to secrete glycosaminoglycans (hyaluronic acid); **expansion of retro-orbital tissue** → infiltrative ophthalmopathy (**exophthalmos**). **the most likely underlying pathogenesis** → **Excessive fibroblast proliferation**
- in case of reduced vision with colour desaturation, the most likely mechanism is → Optic nerve compression**
- Hyperthyroidism → stimulates the beta receptors of the third cranial nerve → stimulates the levator palpebrae superioris muscle → **Pull up the eyelid** → **lid lag and lid retraction**

Which eye signs are specific to Graves' disease?

Eye signs specific to Graves' disease	Eye signs found in most thyrotoxic states
<ul style="list-style-type: none"> • Proptosis • Ophthalmoplegia • Chemosis • Periorbital oedema 	Both lid lag and lid retraction reflect enhanced sensitivity to circulating catecholamines and may therefore be found in most thyrotoxic states.

Prevention

- **Avoid smoking**
- Patients with thyroid eye disease are generally **treated with steroids for one to two weeks prior to starting radioiodine therapy**. Radioiodine treatment → ↑↑ thyroid eye disease → malignant exophthalmos. Prednisolone may help reduce the risk.
- In patients with thyroid eye disease undergoing radioiodine treatment, **post-radioiodine hypothyroidism should be avoided**, because of the risk of **worsening Grave's eye disease**. For this reason, patients are stabilised on a **block replace regimen** before moving to radioiodine therapy.

Smoking is the most important modifiable risk factor for the development of thyroid eye disease

Investigations

- Thyroid function tests: ↓ TSH and ↑ free T3/T4; ↑ TSH receptor antibodies
- **Noncontrast CT scan of the orbits: the initial image of choice**
 - ⇒ assess the risk of future optic nerve compression by enlarged extraocular muscle at the orbital apex.
 - ⇒ measure the of proptosis and retroocular fat accumulation
 - ⇒ helpful in the differential diagnosis
- **MRI** of her orbits: certainly demonstrate **retro-orbital and extraocular muscle inflammation**.

Management

- **Eye protection: local measures** (e.g. artificial tears (saline eye drops), raising the head of the bed at night), topical lubricants to prevent corneal inflammation caused by exposure
- **Mild orbitopathy: local measures are usually effective** to relieve eye symptoms, and **no additional treatment is needed**.
- **Moderate-to-severe orbitopathy** → glucocorticoids is the **initial therapy**.
- **Avoid smoking**
- **Treat hyperthyroidism** (if present): by thionamides, radioiodine, or surgery.
 - ⇒ Radioactive iodine ablation (RAIA) can be used for patients with active **mild** disease. **Moderate-to-severe** is a contraindication to radioiodine therapy.
 - ⇒ Although radioiodine could exacerbate Graves' ophthalmopathy, radioiodine treatment can safely be given to patients with inactive Graves' ophthalmopathy with steroid cover, provided hypothyroidism is avoided.
- **For sight-threatening** (malignant exophthalmos, diplopia and loss of colour vision)
 - ⇒ **The initial treatment is IV glucocorticoids** (dexamethasone, 4 mg IV)
 - ⇒ Surgical orbital decompression may be necessary: performed 1-2 weeks after IV glucocorticoids if the response is poor.

Indications of urgent review by an ophthalmologist

- Unexplained deterioration in vision
- Awareness of change in intensity or quality of colour vision in one or both eyes
 - ⇒ **Impaired perception of colour implies → acute progressive neuropathy.**
- History of eye suddenly 'popping out' (globe subluxation)
- Obvious corneal opacity
- Cornea still visible when the eyelids are closed
- Disc swelling

If there is active Grave's eye disease, then radioiodine therapy is not recommended as it can worsen the eye disease

Thyroid storm (crisis)

In a patient with thyroid storm with high heart rate over 170bpm and low blood pressure the most urgent management is **IV beta-blocker**

Thyrotoxic storm is treated with **beta blockers, propylthiouracil and hydrocortisone**

Overview

- An acute exacerbation of hyperthyroidism that results in a life-threatening hypermetabolic state.
- Thyroid storm is a rare but life-threatening acute exacerbation of thyrotoxicosis.
- Associated with a significant mortality rate (30-50%)
- It is typically seen in patients with established thyrotoxicosis and is rarely seen as the presenting feature.
- Iatrogenic thyroxine excess does not usually result in thyroid storm.

Precipitating factors

- Any acute stressful condition such as surgery or trauma
- Acute infections
- Acute iodine load e.g. CT contrast media
- Postpartum
- When antithyroid drugs are being withdrawn.

Clinical features include

- Altered mental status (confusion, agitation)
- Fever > 38.5C
- Tachycardia
- Nausea, vomiting, and diarrhea
- Jaundice
- Hypertension
- Multisystem decompensation: heart failure, respiratory distress, prerenal failure, abnormal liver function test.

Diagnosis

- Low/undetectable TSH, elevated free T3/T4 (but may not be grossly elevated)

Management

- Transfer the patient to the Intensive Care Unit
- Symptomatic treatment
 - ⇒ Tachycardia: beta blockers, first-line → propranolol
 - ⇒ Hypotension and hypovolemia: fluid resuscitation
 - ⇒ Hyperpyrexia → Paracetamol
 - ⇒ Agitation → chlorpromazine (also can be useful in treating the hyperpyrexia because of its effect in inhibiting central thermoregulation)
- Antithyroid drugs in thyroid storm
 - ⇒ Inhibition of thyroid hormone synthesis: First line → propylthiouracil
 - ⇒ Inhibition of thyroid hormone release (through the Wolff-Chaikoff effect): First line → Potassium iodide solution given at least 1 hour after antithyroid drugs
 - ⇒ Inhibition of peripheral conversion of T4 to T3: Glucocorticoids → First line: hydrocortisone, alternative: dexamethasone
 - ⇒ Inhibition of enterohepatic circulation of thyroid hormones: bile acid sequestrants → cholestyramine
 - ⇒ Plasmapheresis and peritoneal dialysis may be effective in cases resistant to the usual pharmacological measures.

In thyroid storm, treat acutely with propylthiouracil rather than carbimazole

Iodine in CT contrast media can precipitate thyrotoxicosis or thyroid storm

Treatment of thyroid storm, five 'Bs':

1. Block synthesis (i.e. antithyroid drugs);
2. Block release (i.e. iodine);
3. Block T4 into T3 conversion (i.e. high-dose propylthiouracil, propranolol, corticosteroid);
4. Beta-blocker.
5. Block enterohepatic circulation (i.e. cholestyramine).

Thyroid cancer

Epidemiology

- accounts for <1% of all cancer
- commonest in adults aged 40–50
- ♀ are affected more than ♂.

Causes

- Genetic factors
 - ⇒ Medullary carcinoma: associated with MEN2 (RET gene mutations)
 - ⇒ Papillary carcinoma: associated with RET/PTC rearrangements and BRAF mutations
 - ⇒ Follicular carcinoma: associated with PAX8-PPAR-γ rearrangement and RAS mutation
 - ⇒ Undifferentiated/anaplastic carcinoma: associated with TP53 mutation
- Ionizing radiation; associated with papillary carcinoma

Classification

- There are five main types of thyroid carcinoma and their properties are given below:

Cell type	Frequency	Behaviour	Spread	Prognosis
Papillary	80%	Often young females present as "cold nodules" on isotope scanning	Local – Lymph node mets predominate	Excellent
Follicular	10%	More common in females	Haematogenous	Good
Medullary cell	5%	Often familial. Cancer of parafollicular cells (c cell), secrete calcitonin, part of MEN-2	Local and mets	Poor
Lymphoma	2%	*almost always non-Hodgkin lymphomas * Associated with Hashimoto's *often elderly women.	Locally invasive	Poor
Anaplastic	~ 1–2%	Aggressive, Not responsive to treatment, can cause pressure symptoms	Haematogenous	Very Poor

Papillary carcinoma is the most Prevalent type of thyroid cancer, it features **Palpable lymph nodes**, and it has the best **Prognosis** compared to all other types of thyroid cancer.

Medullary thyroid carcinoma (MTC)

- C cells derived from neural crest and not thyroid tissue
- Systemic effects of calcitonin** → flushing/diarrhoea
- The best screening and diagnostic test:** pentagastrin stimulation test . It measures calcitonin levels at 2 and 5 minutes after pentagastrin infusion , and a **rise in calcitonin** is suggestive of medullary thyroid carcinoma.
- Investigations to exclude MEN 2 should be done:
 - ⇒ serum calcium to exclude hyperparathyroidism
 - ⇒ metanephhrines to exclude phaeochromocytoma. **Exclusion of phaeochromocytoma is crucial before thyroidectomy** → abdominal MRI, because any major surgery can precipitate hypertensive crisis due to release of **massive amounts of catecholamines**.
 - ⇒ genetic testing for RET mutation
- Need geniting screening. Germline RET mutation carriers should undergo thyroidectomy before 5 years of age.

Thyroid lymphoma

- Associated with preexisting chronic autoimmune (Hashimoto's) thyroiditis**
- The best choice of therapy is combined chemotherapy with local radiation therapy.**

Features

- May be asymptomatic
- Thyroid nodule: Firm to hard, Typically painless
- Features of local infiltration or compression: recent onset of: hoarseness of voice, dyspnea or dysphagia

Diagnosis

- **Thyroid ultrasound:**
 - ⇒ the initial investigation of choice in small non-symptomatic thyroid mass
 - ⇒ sonographic signs of thyroid cancer
 - Solid or mostly solid hypoechoic nodule(s)
 - Irregular margins
 - Microcalcifications
 - taller than wide
- **Fine-needle aspiration cytology (FNAC):** Confirmatory test
 - ⇒ The appropriate investigation after ultrasound
- Thyroid scintigraphy → decreased or no radiotracer uptake (i.e., hypofunctioning or nonfunctioning nodules, referred to as cold nodules)
- **Thyroid cancer tumor markers**
 - ⇒ **Follicular or papillary thyroid cancer:** Thyroglobulin (Tg): precursor of thyroid hormones; produced exclusively by the thyroid gland. Indicated after total thyroidectomy or RAI therapy
 - ⇒ **Medullary carcinoma:** Calcitonin: A hormone secreted by parafollicular cells, which is the tissue of origin of medullary carcinoma
 - supportive diagnostic marker
 - monitor response to therapy

Medullary thyroid cancer - calcitonin is used for screening, prognosis and monitoring

Follicular thyroid carcinoma VS follicular adenoma.

- Fine-needle aspiration (FNA) biopsy alone cannot distinguish
- The actual diagnosis of follicular thyroid cancer **requires histologic evaluation of the thyroid after surgery** and the identification of tumor capsule and/or vascular invasion.
- **Follicular carcinoma invades the thyroid capsule and vasculature, unlike a follicular adenoma.**

Pathology

- **Papillary thyroid carcinomas:**
 - ⇒ Psammoma bodies (concentric lamellar calcifications)
 - ⇒ "Orphan Annie" eyes nuclei (empty-appearing large oval nuclei with central clearing)
 - ⇒ Nuclear grooves
- **Follicular carcinoma**
 - ⇒ Uniform follicles
 - ⇒ Vascular and/or capsular invasion
- **Medullary carcinoma**
 - ⇒ Ovoid cells of C cell origin and therefore without follicle development
 - ⇒ Amyloid in the stroma (stains with Congo red)
- **Anaplastic thyroid carcinoma**
 - ⇒ Undifferentiated giant cell (i.e., osteoclast-like cell)

"Papi and Moma adopted Orphan Annie:" papillary thyroid cancer is histologically characterized by psammoma bodies and Orphan Annie-eye nuclei.

Medullary carcinoma is composed of C-cells producing Calcitonin and is characterized by amyloid accumulation staining with Congo red.

Which proto-oncogenes is most associated with papillary carcinoma of the thyroid?

- Trk is a proto-oncogene, mutation of which leads to activation of tyrosine kinase receptors.
- Trk activation is thought to play a role in the pathogenesis of papillary thyroid carcinoma

Management: Surgical resection is the primary treatment for thyroid cancer.

- Total thyroidectomy +/- neck dissection as needed (e.g., in patients with regional lymph node spread)
- **Hemithyroidectomy:** Indications
 - ⇒ Small, well-differentiated thyroid carcinoma with all of the following characteristics:
 - Intrathyroidal tumors (i.e., no evidence of extrathyroidal extension)
 - No nodal or distant metastasis
 - No high-risk patient factors
 - ⇒ Preferred option in tumors < 1 cm in size
 - ⇒ An alternative to total thyroidectomy in tumors 1–4 cm in size
- **Contraindications**
 - Intrathyroidal tumor ≥ 4 cm
 - Extrathyroidal spread
 - Distant or nodal metastasis
- **Adjuvant therapy**
 - ⇒ Well-differentiated thyroid cancer
 - Radioactive iodine ablation (RAIA): conducted 4– 6 weeks after total thyroidectomy to destroy remaining thyroid tissue or metastases
 - TSH suppression therapy: → thyroxine after completion of RAIA
 - ⇒ Poorly differentiated thyroid cancer: adjuvant radiation therapy and/or chemotherapy
- **Post-operative thyroid replacement therapy (thyroxine)**
 - ⇒ The aim: titrate the thyroxine dose to suppressed TSH levels:
 - In high risk thyroid cancers: TSH levels should be less than 0.1 mU/L
 - In intermediate risk cancers: TSH can be maintained between 0.1- 0.5
 - In low risk thyroid cancer target TSH to be in 0.5-2.0 range.
 - ⇒ Most patients will require 175 or 200 µg daily.
- **Post-operative follow-up**
 - ⇒ yearly thyroglobulin (Tg) levels to detect early recurrent disease (thyroid is the only source of thyroglobulin).
 - ⇒ **The most appropriate investigation at annual follow-up for papillary thyroid cancer.**
 - **Ultrasound scan is the most sensitive investigation for the detection of locally recurrent papillary carcinoma.**
 - Other investigations should be considered if ultrasound scan is negative or distant metastases are suspected. (SCE. Questions sample. Mrcpuk.org).

Thyroid cancer treatment → Thyroidectomy and neck dissection with postoperative radioiodine ablation

Thyroid cancer associated with Graves' disease is not uncommon and usually due to papillary carcinoma and must be considered in suspicious/expanding nodules rather than attributing purely to Graves' disease.

- hyperthyroidism with prominent nodule which is 'cold' on uptake scanning is highly suggestive of thyroid carcinoma and the most likely diagnosis is Graves' disease (periorbital puffiness and thyroid bruit) associated with papillary thyroid carcinoma.

The association of Horner's syndrome and a thyroid nodule suggest invasion of the sympathetic chain and suggest that this thyroid nodule is malignant.

Which familial condition carries an increased risk of papillary carcinoma of the thyroid ?

- Gardner's syndrome (intestinal tumours & lipomas. Also Osteomas & fibromas). carries an increased risk of papillary carcinoma

Which test is most useful in the assessment of airflow obstruction due to the retrosternal goitre?

- Flow volume curve

Thyroid nodule and fine-needle aspiration

Epidemiology

- About 50% of the general population have single or multiple thyroid nodules, whereas the incidence of thyroid malignancy is 2-4%.

Thyroid ultrasound

- Ultrasonographic criteria associated with higher risk of malignancy:
 - Low echodensity (Hypoechoogenicity)
 - Microcalcifications: the most predictive feature of malignancy**
 - Irregular borders (poorly-defined margin)
 - Increased intranodular vascularity: ($\uparrow\uparrow$ marginal blood flow → benign adenoma, $\uparrow\uparrow$ intranodular blood flow → thyroid cancer)
 - Absence of a halo
 - Taller-than-wide configuration on transverse view
- Referral of a thyroid nodule: (British Thyroid Association (BTA) guidelines)

Same day	Urgent	Non-Urgent	Managed by GP
Stridor associated with thyroid lump	Palpable cervical lymph nodes	Patient with hyper or hypothyroidism refer to endocrinologist	No change in size over years
	Rapidly enlarging (days-weeks)	Lump enlarging over months	No known risk factors
	Presence of risk factors for thyroid cancer	Sudden pain and enlarged mass (bleeding in a cyst)	<1cm, incidental thyroid nodule
	Hoarseness of voice		
	Nodule in a child		

- Ultrasound "U" classification of thyroid nodules

Classification	Criteria
U1 (normal)	- no nodules
U2 (benign)	<ul style="list-style-type: none"> - hyperechoic or isoechoic with a halo - cystic change with ring down artifact (colloid) - microcystic or spongiform appearance - peripheral egg-shell calcification - peripheral vascularity
U3 (indeterminate)	<ul style="list-style-type: none"> - solid homogenous markedly hyperechoic nodule with halo (follicular lesions) - hypoechoic with equivocal echogenic foci or cystic change - mixed or central vascularity
U4 (suspicious)	<ul style="list-style-type: none"> - solid hypoechoic (compared with thyroid) - solid very hypoechoic (compared with strap muscles) - hypoechoic with disrupted peripheral calcification - lobulated outline
U5 (malignant)	<ul style="list-style-type: none"> - solid hypoechoic with a lobulated or irregular outline and microcalcification (papillary carcinoma) - solid hypoechoic with a lobulated or irregular outline and globular calcification (medullary carcinoma) - intranodular vascularity - taller than wide axially (AP>ML) - characteristic associated lymphadenopathy

- The need for Fine Needle Aspiration Cytology (FNAC) according to US:

U1-2	not requiring FNAC, unless the patient has a statistically high risk of malignancy
U 3 - 5	FNAC should be done

Fine needle aspiration (FNA)

- the gold standard diagnostic tool for thyroid nodules. **but follicular neoplasia can only be diagnosed histologically.**

- Diagnostic categories from FNAC (The royal college of pathologist classification)

	Category	Action
Thy 1	Non-diagnostic. Inadequate	Repeat sampling, using US if necessary
Thy 2	Non-neoplastic	Two samples, 3–6 months apart, showing benign appearances are indicated to exclude neoplasia. If rapid growth/pressure effects/high risk, diagnostic lobectomy may be indicated
Thy 3 (Thy3f)	(i) Follicular lesions	Lobectomy (diagnostic hemithyroidectomy) (because follicular adenoma or follicular carcinoma cannot be distinguished on cytology alone) with completion thyroidectomy if malignant (up to 20% risk of malignancy)
Thy 3 (Thy3a)	(ii) atypical features, other suspicious findings	Many Thy3a cases reflect suboptimal specimens → Discussion at thyroid cancer MDT → Repeat FNAC
Thy 4	Suspicious of malignancy	Surgical excision for differentiated tumour (80% risk of malignancy) (diagnostic hemithyroidectomy)
Thy 5	Diagnosis of malignancy	Surgical excision for differentiated thyroid cancer (>95% risk of malignancy). Radiotherapy/ chemotherapy for anaplastic thyroid cancer, lymphoma/metastases

Calcium metabolism

Overview

- The average adult store of calcium is approximately **1–2 kg**.
- Recommended daily dietary calcium requirement: **1 – 1.5 g per day**.
- Bones are the major storage site of calcium (**99%**)
- Plasma Ca²⁺ exists in three forms:**
 - Ionized/ free (~45%, active form): The most important form in regulation of body functions
 - Bound to albumin (~40%)
 - Bound to anions (~15%)

Actions of the Hormones Involved in Calcium Homeostasis

HORMONE	EFFECT ON BONES	EFFECT ON GUT	EFFECT ON KIDNEYS
Parathyroid hormone →↑Ca ⁺⁺ , ↓PO ₄ levels in blood	↑osteoclastic activity	Indirect effects via ↑calcitriol from 1-hydroxylation	↑Ca ⁺⁺ resorption and PO ₄ excretion, activates 1-hydroxylation → ↑ conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol
Calcitriol (vitamin D) ↑Ca ⁺⁺ , ↑PO ₄ levels in blood	↑osteoclastic activity	↑Ca ⁺⁺ and PO ₄ absorption	↑renal tubular reabsorption of Ca ⁺⁺ and PO ₄
Calcitonin causes ↓Ca ⁺⁺ , ↓PO ₄ levels in blood when hypercalcemia is present	Inhibits osteoclast resorption	No direct effects	Promotes Ca ⁺⁺ and PO ₄ excretion

Effects of pH and albumin changes on Ca²⁺ homeostasis

- Ca²⁺ competes with H⁺ to bind to albumin
- ↑ pH (less H⁺) → albumin binds more Ca²⁺ → ↓ ionized Ca²⁺ (eg, cramps, pain, paresthesias, carpopedal spasm) → ↑ PTH
- ↓ pH (more H⁺) → albumin binds less Ca²⁺ → ↑ ionized Ca²⁺ → ↓ PTH
- Even if the total extracellular fluid (ECF) calcium stays constant, the bound percentage can vary, increasing with alkalosis and decreasing with acidosis. So if the free concentration percentage falls, hypocalcemia symptoms may occur even though the total measured ECF calcium has not changed.
- Hypoproteinemia (due to, e.g., nephrotic syndrome, liver cirrhosis, severe malnutrition, malabsorption) → ↓ total Ca²⁺ level but ionized Ca²⁺ level is unaffected; → factitious hypocalcemia (*Pseudohypocalcemia*)

To remember the effect pH has on PTH, think: ↑ pH = ↑ PTH and ↓ pH = ↓ PTH.

Absorption

- **Intestinal absorption of calcium is facilitated by →1,25 dihydroxy-vitamin D**, which stimulates the microvillous membrane of the enterocyte to synthesise the calcium-binding carrier protein necessary for active calcium ion absorption.
- 99% of filtered calcium is reabsorbed in the kidneys, around 55% in the proximal convoluted tubule

Excretion

- Calcitonin is the most important factor regulating calcium excretion.
- Calcitonin is secreted by the parafollicular cells of the thyroid gland and responds to raised calcium levels by inhibiting bone resorption and increasing renal excretion
- calcium excretion is heavily influenced by sodium excretion. Low-sodium diets tend to decrease Ca excretion and vice versa.
- The concentration of calcium in urine reflects serum calcium.

All patients should maintain a **daily total calcium intake** (diet plus supplement) of **1000 mg** (for ages 19 to 70 years) to **1200 mg** (for women ages 51 through 70 years and all adults 71 years and older)

Hypercalcaemia

hyperparathyroidism → ↑Ca⁺⁺, ↓PO₄ levels

90% of hypercalcemia are caused by primary hyperparathyroidism and

Thiazides cause hypercalcaemia, might unmask underlying primary hyperparathyroidism (PHPT), as they cause mild hypercalcemia by reducing urinary calcium excretion.

Definition

- Corrected calcium of more than 2.6 mmol/l.

Causes

- **Primary hyperparathyroidism** (normal or ↑ PTH, ↑ serum Ca⁺⁺, ↓PO₄): **the commonest cause**
- **Malignancy**
 - ⇒ Hypercalcaemia occurs in 20% to 30% of patients with cancer.
 - ⇒ **Most common cause: paraneoplastic production of PTHrP** (e.g., squamous cell carcinomas of the lung, head, and neck; breast, ovarian, bladder, and renal cancer; lymphoma and leukemia)
 - ⇒ **Osteolytic metastases** (e.g., multiple myeloma, breast cancer, lymphoma and leukemia, renal cancer) → **Skeletal survey is the best initial investigation to contribute to the underlying diagnosis**
 - ⇒ **Paraneoplastic production of 1,25-dihydroxyvitamin D**: e.g., lymphoma.
 - ⇒ **suppressed PTH, hypercalcaemia without hypophosphataemia**. phosphate will be low in PTHrP-mediated hypercalcaemia.
- **Familial hypocalciuric hypercalcaemia**: autosomal dominant mutations in the calcium sensing receptor gene, leading to calcium hyposensitivity (↑ serum Ca⁺⁺, ↑ or normal PTH, ↓urine Ca⁺⁺).
- **Vitamin D intoxication**: due to ↑ supplementation, ↑sun exposure →↑ vitamin D production → ↑vitamin D (1,25 OH cholecalciferol), ↑ serum Ca⁺⁺, normal or ↓ PTH)
- **Drug induced**
 - ⇒ Thiazides → ↓ excretion → hypercalcaemia (but furosemide → hypocalcaemia)
 - ⇒ calcium containing antacids
 - ⇒ **lithium** →↑release of PTH
 - ⇒ Vitamin A toxicity (including analogs used to treat acne)
 - ⇒ Theophylline toxicity
- **Tertiary hyperparathyroidism**: Usually seen in patients with ESRD
 - ⇒ Renal failure → chronic secondary hyperparathyroidism → autonomous (unregulated) activation of one or more parathyroid gland. (Note that secondary hyperparathyroidism is a response to hypocalcaemia, not a cause of hypercalcaemia).
- **Hyperthyroidism**: ↑ serum Ca⁺⁺, normal or ↓ PTH, ↓ TSH
- **Milk-alkali syndrome**: ↑ serum Ca⁺⁺, normal or ↓ PTH
 - ⇒ Cased by consumption of large amounts of calcium carbonate
 - ⇒ Presents with a triad of **hypercalcemia, metabolic alkalosis (↑bicarbonate)**, and **acute kidney injury**
- **Sarcoidosis** → activated pulmonary macrophages → ↑vitamin D →↑intestinal absorption of Ca → ↑Ca
- **Prolonged immobilisation**: ↑ serum Ca⁺⁺, nondetectable PTH
 - ⇒ Lack of weight-bearing activities → osteoclast activation → bone demineralization → hypercalcemia
- **Paget's disease**: ↑ serum Ca⁺⁺, nondetectable PTH
- **Williams' syndrome**: a rare genetic disease affecting chromosome 7 and characterised by hypercalcaemia, unusual "elfin" appearance, with a low nasal bridge, anxiety and learning disability.
- **Acromegaly**
- **Dehydration**
- **Addison's disease**
- **Infections**: HIV, histoplasmosis

Differentiate between hypercalcaemia in primary hyperparathyroidism and malignancy:

- in primary hyperparathyroidism
 - ⇒ Parathyroid hormone is elevated or normal
 - ⇒ calcium level is often $< 3 \text{ mmol/l}$
 - ⇒ Hypercalcaemia is often asymptomatic and might have been present for months or years.
 - ⇒ Chronic symptoms are more consistent with hyperparathyroidism, whereas more recent onset of symptoms suggests malignancy.
- in malignancy
 - ⇒ patients are usually acutely ill
 - ⇒ often with neurological symptoms
 - ⇒ calcium level is usually $> 3 \text{ mmol/l}$
 - ⇒ Parathyroid hormone is suppressed
 - ⇒ Cancer (eg lung, breast or myeloma) is often clinically apparent.

Features

- **Bones:** Bone pain, malaise, fatigue, muscle weakness
- **Stones:** Nephrolithiasis
- **Groans:** abdominal pain, constipation, peptic ulcer disease, pancreatitis
- **Thrones:** polydipsia and polyuria
- **Psychic moans:** impaired concentration, confusion, hyporeflexia, depression
- Cardiovascular manifestations: **short QT interval** → ↑ risk of cardiac arrhythmias.

Mechanism of volume depletion in hypercalcaemia

- ↑calcium → ↓effect of ADH on the collecting duct → nephrogenic diabetes insipidus.
- ↑calcium → osmotic diuresis.

The presentation of hypercalcemia includes **stones** (nephrolithiasis), **bones** (bone pain, arthralgias), **thrones** (increased urinary frequency), **groans** (abdominal pain, nausea, vomiting), and **psychiatric overtones** (anxiety, depression, fatigue).

Hypercalcemia can cause pancreatitis. Hypocalcemia in patients with pancreatitis suggests pancreatic necrosis.

Management

- Supportive care
 - ⇒ **Hydration**
 - ⇒ Identify and treat the underlying cause
 - ⇒ Reduce dietary intake of calcium
 - ⇒ Avoid; thiazides; lithium
- **Severe hypercalcemia ($\text{Ca}^{++} > 3.5 \text{ mmol/L}$) and symptomatic moderate hypercalcemia ($\text{Ca}^{++} 3.0\text{--}3.5 \text{ mmol/L}$):**
 - ⇒ **Start IV fluid therapy with 0.9% NaCl.** the initial management of hypercalcaemia
 - ⇒ **Loop diuretics in association with saline infusion** to increase calcium excretion.
 - It may be useful in patients who cannot tolerate aggressive fluid rehydration (e.g. heart failure and renal impairment) or if more rapid lowering of serum calcium is desired,
 - ⇒ **Bisphosphonates (I.V)** to inhibit osteoclast activity → ↓ bone turnover.
 - **The most appropriate next step** after hydration
 - take 2-3 days to work with maximal effect being seen at 7 days

- Options include **pamidronate** disodium and **zoledronic acid**, which are both administered as a single dose.
- ⇒ **Calcitonin** to inhibit osteoclast activity and enhance urinary excretion of calcium.
 - **quicker effect than bisphosphonates**
 - **Refractory hypercalcaemia of malignancy may be treated with subcutaneous calcitonin if therapy with fluids and pamidronate fails**
 - calcitonin use is limited by its transient effect, association with anaphylaxis and availability.
- ⇒ **Steroids** in sarcoidosis
- ⇒ Consider haemodialysis for refractory life-threatening hypercalcemia or if other therapies are contraindicated

Thiazide diuretics enhance Tubular calcium uptake: Discontinue them in hypercalcemia. Loop diuretics Lose calcium: They may be used to treat fluid overload in patients with hypercalcemia.

Familial hypocalciuric hypercalcemia (FHH)

Pathophysiology

- **autosomal dominant** inactivating **mutation in the CaSR gene** → decreased sensitivity of G-coupled calcium-sensing receptors in parathyroid glands and kidneys; higher reabsorption of Ca^{2+} in the kidney → hypocalciuria with mild hypercalcemia and normal or increased PTH levels

Features

- Usually asymptomatic (often diagnosed incidentally)
- Neonatal hypocalcemia in children of mothers with FHH (e.g., paresthesias, muscle spasms, seizures)

Diagnosis

- Hypercalcemia and inappropriately normal or increased PTH
- Hypocalciuria
- a two-step diagnostic procedure is recommended (The diagnostic sensitivity of this setup is 98%)
 - ⇒ First, the **calcium/creatinine clearance ratio** is measured from a 24-h urine.
 - ⇒ Second, all patients with calcium/creatinine clearance ratio of 0.020 or less are tested for mutations in the **CASR gene** (**Request calcium sensing receptor mutational analysis**)
- No evidence of end organ damage (normal renal function, absence of nephrolithiasis, no evidence of bone disease)

Treatment

- No treatment necessary

Hypocalcaemia

Causes

- Vitamin D deficiency (osteomalacia) (**Osteomalacia causes hypocalcaemia associated with a low serum phosphate**)
- Chronic renal failure
- Hypoparathyroidism (e.g. post thyroid/parathyroid surgery)

- Pseudohypoparathyroidism (target cells insensitive to PTH) (short fourth finger, round face, and mental retardation)
- Rhabdomyolysis (initial stages)
- **Magnesium deficiency:** (Magnesium is needed to release PTH from the gland)
 - ⇒ Hypomagnesemia → ↓ PTH secretion or induces PTH resistance → hypocalcemia
 - ⇒ **Causes:**
 - **ileostomies** → magnesium loss through stomas → **hypomagnesaemia**
→ ↓ PTH → hypocalcaemia that is resistant to an increased provision of calcium
 - end organ PTH resistance
 - Long term alcoholism → significant falls in magnesium → persistently decreased calcium despite replacement
 - **Omeprazole and PPI** → ↑ GI magnesium losses → **hypomagnesaemia** → impairs the calcium sensing on the parathyroid cells → hypoparathyroidism → hypocalcaemia.
- Hyperphosphatemia: Phosphate binds with the calcium and lowers it.
 - ⇒ ↓ Renal excretion of phosphate (e.g., impaired renal function)
 - ⇒ Increased phosphate intake (e.g., oral supplements, enemas)
 - ⇒ Increased tissue breakdown (e.g., tumor lysis syndrome, rhabdomyolysis, crush injury)
- Fat malabsorption: This binds calcium in the gut.
- Massive blood transfusion
 - ⇒ anticoagulant **citrate** in the bags → **citrate accumulation** in blood → chelates (binds to) circulating ionized calcium (iCa) → ↓ plasma iCa.
- Acute pancreatitis may also cause hypocalcaemia.
- Contamination of blood samples with EDTA may also give falsely low calcium levels
- Pseudohypocalcemia: Due to gadolinium contrast agent or hypoalbuminemia
- Hyperventilation: Redistribution of calcium
- Drug induced: e.g: Loop diuretics increase renal calcium excretion.

Hypocalcemia is most often due to hypoparathyroidism or vitamin D deficiency (e.g., malabsorption, chronic kidney disease).

Magnesium deficiency causes hypocalcaemia

- ↓↓ calcium and phosphate + ↑↑ alkaline phosphatase → **Osteomalacia**
- **normal** calcium and phosphate + ↑↑ alkaline phosphatase → **Paget's disease**
- Serum **biochemistry is normal** in **osteoporosis**, although alkaline phosphatase can be elevated following a fracture.

As extracellular calcium concentrations are important for muscle and nerve function many of the features seen in hypocalcaemia seen as a result of neuromuscular excitability

Features

- **Tetany:** increased neuromuscular excitability (when caused by respiratory alkalosis = hyperventilation-induced tetany): muscle twitching, cramping and spasm
 - ⇒ **Paresthesias:** typically tingling or pins-and-needles sensation in extremities and/or in the **perioral area**
 - ⇒ **carpopedal spasm** (wrist flexion and fingers drawn together)
 - ⇒ Bronchospasm, laryngospasm

- Seizure
- If chronic: depression, cataracts
- **Maneuvers to elicit latent tetany on physical exam**
 - ⇒ **Trousseau sign:** ipsilateral carpopedal spasm occurring several minutes after inflation of a blood pressure cuff. **seen in around 95% of patients** with hypocalcaemia and around 1% of normo-calcaemic people
 - ⇒ **Chvostek sign:** short contractions (twitching) of the facial muscles elicited by tapping the facial nerve below and in front of the ear. **seen in around 70% of patients** with hypocalcaemia and around 10% of normo-calcaemic people
- Hyperreflexia
- ECG changes
 - ⇒ Common: Corrected QT interval prolongation
 - ⇒ Rare: Atrial fibrillation or torsade de pointes

Parathyroid hormone is the single most useful test in determining the cause of hypocalcaemia

Hypocalcaemia: Trousseau's sign is more sensitive and specific than Chvostek's sign

Signs of neuromuscular irritability (e.g., paresthesias, spasms and cramps) are the most characteristic features of hypocalcemia.

Diagnosis

- Confirm true hypocalcemia: Measure total and ionized calcium
- **Serum intact PTH: the best initial study**
- **Laboratory findings in hypocalcemia**

Findings	Conditions
Low PTH, ↑ Phosphate	Hypoparathyroidism (e.g., postsurgical)
High PTH, ↑ Phosphate	Hyperphosphatemia Pseudohypoparathyroidism
High PTH, ↑ Phosphate, ↑ Creatinine	Chronic kidney disease
High PTH, ↓ Magnesium	Malabsorption or alcoholism

Management

- **Mild and/or chronic hypocalcemia:** no symptoms or only mild neuromuscular irritability (e.g., paresthesias): Oral calcium supplementation
- **Severe and/or symptomatic hypocalcemia:** e.g., tetany, seizures, prolonged QT interval, serum calcium $\leq 7.5 \text{ mg/dL} (< 1.9 \text{ mmol/L})$
 - ⇒ intravenous **calcium gluconate**, 10ml of 10% solution over 10 minutes. intravenous **calcium chloride** is more likely to cause local irritation
 - ⇒ **ECG monitoring**
 - **Treatment of the underlying condition**
 - ⇒ Hypoparathyroidism → Calcium and vitamin D supplementation
 - ⇒ Secondary to loop diuretics: consider discontinue loop diuretic and change medication to thiazides.
 - ⇒ Vitamin D deficiency: vitamin D supplementation
 - ⇒ Hypomagnesemia-induced hypocalcemia: magnesium supplementation

IV calcium can trigger life threatening arrhythmias in patients simultaneously receiving cardiac glycosides (digoxin or digitoxin).

Daily calcium intake of between 700 and 1200mg should be advised

Magnesium (Mg)

Overview

- Mg is the second most abundant intracellular cation in the body (after potassium)
- 99% of total body magnesium is intracellular or bone-deposited, with only 1% present in the extracellular space.
- Normal plasma magnesium → (0.7-0.9 mmol)
- Dietary magnesium is absorbed by the ileum of the small intestine, stored mainly in the bones, and excreted by the kidneys.

Dietary sources of magnesium

- green vegetables, fruits, fish, fresh meat, and cereals.

Recommended daily intake of magnesium

- Adult females: 280 mg/day normally, increased to 350 mg/day during pregnancy and lactation
- Adult males: 350 mg/day

Magnesium homeostasis

- About 60% of magnesium in the serum is **free**, whereas 33% is bound to proteins,
- Magnesium status is regulated by the intestines, which control absorption; the kidneys, which control excretion; and bone, which is the major storage site.
- Intestinal absorption and renal excretion are mediated by the selective magnesium channel **TRPM6**.
- magnesium uptake and release from tissues outside the intestines and kidneys is controlled by **TRPM7**.
- most of the absorption taking place in the colon.
- Hormones such as glucagon, catecholamines, and parathyroid hormone (PTH) can mobilise magnesium from bone and other tissues.
- hormones such as **insulin**, antidiuretic hormone (**ADH**), and **thyroid hormone** promote magnesium uptake and storage.
- **The main controlling factors in magnesium homeostasis** → GIT absorption and renal excretion.

⇒ Renal reabsorption

- the major site of reabsorption is the loop of Henle,
- Unlike most ions, the majority of magnesium is not reabsorbed in the proximal convoluted tubule (PCT). **the thick ascending limb (TAL) of the loop of Henle is the major site of reabsorption (60-70%).**
- In the TAL, magnesium is **passively** reabsorbed with calcium through paracellular tight junctions
- Claudins are the major components of tight-junction strands in the TAL, where the reabsorption of magnesium occurs
- In the **distal convoluted tubule (DCT)**, magnesium is reabsorbed via an **active**, transcellular process that is thought to involve **TRPM6**
 - ❖ The TRPM6 channel is embedded in the membrane of epithelial cells of large intestine, distal convoluted tubules, lungs, and testes.

Uses for magnesium include:

- polymorphic ventricular tachycardia (torsade de pointes),
- acute asthma
- prevention/treatment of seizures in pre-eclampsia.
- **Magnesium salts can be given as laxatives**

Hypomagnesaemia

Replace magnesium before correcting hypokalaemia.

Hypomagnesaemia prevents potassium absorption

Definition

- magnesium below 0.7 mmol/L

Causes

- **Gastrointestinal**
 - ⇒ Inadequate intake (e.g., anorexia nervosa, prolonged fasting): **the most common cause**
 - ⇒ Malnutrition
 - ⇒ Malabsorption
 - ⇒ Gastric bypass surgery, small bowel bypass surgery, short bowel syndrome
 - ⇒ Vomiting, nasogastric suction
 - ⇒ Acute and chronic diarrhea
 - ⇒ Chronic inflammatory bowel disease
 - ⇒ Acute pancreatitis
 - ⇒ Intestinal fistula
 - ⇒ **Total parenteral nutrition**
 - ⇒ Refeeding syndrome
- **Renal**
 - ⇒ Diuresis
 - ⇒ ATN
 - ⇒ Congenital conditions
 - Bartter syndrome
 - Gitelman syndrome
 - Familial hypomagnesemia with hypercalciuria and nephrocalcinosis
 - Congenital magnesium wasting
- **Endocrine**
 - ⇒ SIADH
 - ⇒ Hyperaldosteronism
 - ⇒ Hyperparathyroidism
 - ⇒ Hyperthyroidism
- **Intracellular shift**
 - ⇒ Post myocardial infarction
 - ⇒ Post parathyroidectomy
 - ⇒ Recovery from diabetic ketoacidosis (K^+ and PO_4^{2-} also enter cells)
 - ⇒ Refeeding syndrome (PO_4^{2-} also enters cells),
 - ⇒ Acute pancreatitis.

- **Drug-induced:**
 - ⇒ **Diuretics**
 - ⇒ **Ciclosporin** and **cisplatin** → ↓ renal reabsorption and ↑ renal excretion of Mg²⁺
 - ⇒ Insulin → ↑ intracellular uptake of Mg²⁺ → hypomagnesaemia.
 - ⇒ **Antibiotics** such as aminoglycosides, gentamicin, and tobramycin inhibit renal reabsorption in the loop of Henle.
 - ⇒ **cardiac glycosides**, Digitalis → ↑ intracellular sodium and calcium → displacement and loss of magnesium.
 - ⇒ **Amphotericin B**
 - ⇒ **Colorectal cancer treatment with cetuximab/panitumumab** → inhibits extracellular growth factor receptor (EGFR) → ↓ TRPM6 → **hypomagnesemia**.
 - ⇒ **Omeprazole (PPIs)** → ↓ intestinal Mg²⁺ absorption through TRPM6 and produce renal magnesium wasting by an unknown mechanism. **hypomagnesaemia** → hypoparathyroidism → hypocalcaemia.
 - The reasons for this are unclear, but it may be due to reduced uptake of Mg²⁺ ions in the gut. Omeprazole reduces acid production and raises stomach PH. An acid environment can aid release of metal ions from their binding sites in food molecules which facilitate absorption.
- **Metabolic acidosis**
 - ⇒ Osmotic diuresis, which occurs in diabetic ketoacidosis, leads to renal magnesium wasting.
 - ⇒ Chronic metabolic acidosis → ↓ renal TRPM6 expression in the DCT → ↓ Mg reabsorption → ↓ serum Mg.
- **Hypercalcaemia**
 - ⇒ Hypercalcemia → activation of **calcium-sensing receptor (CaSR)** → ↓ Mg reabsorption
 - ⇒ Calcium competes with magnesium for uptake in the loop of Henle, and an increase in the filtered calcium load can impair magnesium reabsorption.
- **Burns**
- **Chronic alcohol use**
- **Genetic diseases**
 - ⇒ **Hypomagnesemia with secondary hypocalcemia (HSH):**
 - Autosomal recessive
 - caused by mutations in the TRPM6 gene → ↓↓ intestinal magnesium reabsorption → ↓↓ serum magnesium → ↓↓ (PTH) → ↓↓ serum calcium levels (hypocalcemia).
 - manifests in early infancy with generalized convulsions refractory to anticonvulsant treatment or with other symptoms of increased neuromuscular excitability, such as muscle spasms or tetany.
 - Laboratory evaluation reveals extremely low serum magnesium and serum calcium levels.

Features

General

- lack of appetite.
- Lethargy
- fatigue

Neuromuscular hyper-excitability

- muscle weakness including fasciculations
- changes in personality
- paraesthesia
- tetany
- seizures

Cardiac

- arrhythmias (ECG features similar to those of hypokalaemia) typically QT prolongation.
- exacerbates digoxin toxicity

Electrolytes

- $\downarrow \text{Mg} \rightarrow \downarrow \text{PTH secretion} + \uparrow \text{PTH resistance} \rightarrow \text{hypocalcaemia}$
- Hypokalemia (in 40-60%) ($\downarrow \text{Mg} \rightarrow \uparrow \text{renal potassium wasting}$)

Complications

- Cardiac arrest
- Seizures

Investigation

- Serum magnesium level do not accurately reflect total body magnesium status. only 1% of magnesium is found in the extracellular fluid
- There is no accurate laboratory test to determine total body magnesium
- Urine Mg excretion is a useful guide. When there is inadequate intake or malabsorption, the kidneys would normally conserve Mg, giving urine Mg concentrations $< 7 \text{ mmol/24 hours}$. The reference range is around 2-7 mmol/24 hours.

Treatment

- Repletion should be considered in all patients with symptoms consistent with hypomagnesemia, including patients with normal serum magnesium levels.
- $<0.4 \text{ mmol/l}$
 - ⇒ intravenous replacement is commonly given. An example regime would be 40 mmol of magnesium sulphate over 24 hours
- $>0.4 \text{ mmol/l}$
 - ⇒ oral magnesium salts (10-20 mmol orally per day)
 - ⇒ diarrhoea can occur with oral magnesium salts

Parenteral administration of magnesium can reduce serum calcium levels, which can worsen preexisting hypocalcemia.

Hypermagnesaemia

Overview

- Mg above the reference range 0.7-1.5 mmol/L.
- Hypermagnesaemia is much less common than hypomagnesaemia and is often iatrogenic in cause.

Causes

- Iatrogenic:

- ⇒ Treatment with magnesium sulphate to prevent/treat seizures in patients with eclampsia or pre-eclampsia
- ⇒ Treatment with Mg containing antacids
- ⇒ Use of citrate-glucuronic acid solutions to dissolve renal calculi either through bladder irrigation or via a nephrostomy tube
- ⇒ Over-zealous IV treatment of hypomagnesaemia
- ⇒ Chronic use of Mg-containing enemas.
- **Other causes:**
 - ⇒ **Acute or chronic renal failure**
 - release of Mg from tissues,
 - Mg in dialysate,
 - Mg in phosphate binding drugs
 - ⇒ Familial hypocalciuric hypercalcemia.

Lithium can cause **hypermagnesaemia**

Features

- **Mild hypermagnesaemia** (1.5-2.5 mmol/L) - symptoms uncommon
- **Moderate hypermagnesaemia** (2.5-5.0 mmol/L) - symptoms develop including hypotension, prolonged PR and QRS intervals on ECG, areflexia
- **Severe hypermagnesaemia** (>5.0 mmol/L) - at risk of respiratory paralysis through inhibition of acetylcholine release and cardiac arrest.

Treatment

- If mild/moderate and iatrogenic, often it is enough to identify and stop the cause.
- In an emergency, dialysis or administration of IV calcium glucuronate (10 ml of 10%) will reduce the effects of hypermagnesaemia.

Vitamin D (calciferol)

Sources

- Vitamin D2 (ergocalciferol): plants
- Vitamin D3 (cholecalciferol): dairy products, can be synthesised by the skin from sunlight (the main natural source).

Vitamin D synthesis

1. **Liver:** cholesterol → 7-dehydrocholesterol (provitamin D3) Enzyme: cholesterol dehydrogenase
2. **Skin**
 - ⇒ Storage of 7-dehydrocholesterol
 - ⇒ Cleavage of 7-dehydrocholesterol via irradiation with UV light → cholecalciferol (in the stratum basale)
3. **Liver:** hydroxylation of cholecalciferol to 25-hydroxyvitamin D (25-OH D3, calcidiol)
4. **Kidneys:** 1α-hydroxylase hydroxylates 25-hydroxyvitamin D → 1,25-dihydroxyvitamin D

Transport to target cells: vitamin D-binding protein (DBP)

Storage: as 25-hydroxycholecalciferol, mainly in adipose tissue (25-OH D3)

Active form: 1,25-dihydroxyvitamin D (1,25-(OH)₂ D3, calcitriol)

Regulation of vitamin D synthesis: via regulation of 1α-hydroxylase activity in proximal convoluted tubule

- ↓ Calcium, ↓ phosphate, and ↑ PTH → ↑ 1α-hydroxylase activity → ↑ 1,25-dihydroxyvitamin D biosynthesis
- ↑ Calcium, ↑ phosphate, and ↑ 1,25-dihydroxyvitamin D (feedback inhibition) → ↓ 1α-hydroxylase activity → ↓ 1,25-dihydroxyvitamin D biosynthesis

Functions

- ↑ plasma calcium and plasma phosphate
 - ⇒ ↑ intestinal absorption of magnesium and phosphate
 - vitamin D → ↑ calbindin (an intestinal transporter of calcium) → ↑ calcium absorption from the small intestine.
 - ⇒ ↑ renal tubular reabsorption of calcium and phosphate
- ↑ osteoclastic activity
- ↑ calcium deposition in the extracellular matrix of bone.
- **Suppression of synthesis of type 1 collagen.** This is balanced by upregulation of osteocalcin, the balance of these changes is an increase in bone mineralisation.
- Vitamin D is recognised to modulate cytokine production and may have a role in the treatment of inflammatory disorders in the future. One example is **decreased production of IL6** in response to vitamin D supplementation.

Vitamin D deficiency

Definition

- serum 25-hydroxyvitamin D <50 nanomole/L (<20 nanograms/mL).

Epidemiology

- The most common nutritional deficiency worldwide
- In UK around 5 % of adults and 8 - 24% of children may have low vitamin D status.

Features and complications:

- Rickets: seen in children
 - ⇒ Radiographs of the limbs will demonstrate **epiphyseal widening with metaphyseal fraying.**
- Osteomalacia: seen in adults
 - ⇒ **It classically presents in the female Asian population whose clothing offers little exposure to sunlight.**
 - ⇒ **Proximal myopathy** is often a presenting feature of osteomalacia
 - ⇒ increasing falls
 - ⇒ The phosphate and calcium are usually low normal, and the alkaline phosphatase is high
 - ⇒ Elevated PTH (secondary hyperparathyroidism to maintain the normal calcium.)
- Symptoms of hypocalcemia (e.g., tetany)

Diagnosis

Measurement of serum 25-OH vitamin D is the best way of estimating vitamin D status.

Serum Vit D	Response
Optimal: > 75nmol/l	Nothing
Adequate: 50--75nmol/l	provide reassurance and give advice on maintaining adequate vitamin D levels through safe sunlight exposure and diet
Insufficiency: 30-49nmol/l	treatment is advised in patients with fragility fracture, osteoporosis, symptoms suggestive of vitamin D deficiency, reduced exposure to sunlight, raised PTH, conditions associated with malabsorption
Deficiency: < 30nmol/l	treatment recommended

Treatment (loading doses followed by regular maintenance therapy).

- **Loading dose:**

- **Loading dose:**
 - ⇒ a total of approximately **300,000 IU vitamin D, given either as separate weekly or daily doses over 6 to 10 weeks**
 - Regimes include:
 - ❖ 50,000 IU given weekly over 6 weeks **OR**
 - ❖ 4,000 IU given daily over 10 weeks

- **Maintenance dose**

- **Maintenance dose**
 - ⇒ vitamin D in doses equivalent to 800–2000 IU daily (occasionally up to 4,000 IU daily), given either daily or intermittently at higher doses.

- **Assess his calcium intake:**

- **Assess his calcium intake:**
 - ⇒ co-prescription of a calcium supplement may be required if the nutritional intake is less than 800mg daily.
 - ⇒ In patients with good calcium intake and normal serum calcium, giving oral calcium may lead to adverse cardiovascular outcomes, due to accelerated tissue and vascular calcification.

Adverse effects

- **Vitamin D toxicity (hypercalciuria and hypercalcemia)**

- **Causes**

- **Causes**
 - Oversupplementation
 - Granulomatous disorders (e.g., sarcoidosis): due to increased 1 α -hydroxylase activation in epithelioid macrophages → increased 1,25-dihydroxyvitamin D synthesis

- **Clinical features**

- **Clinical features**
 - Hypercalcemia, hypercalciuria
 - Loss of appetite
 - Stupor

Vitamin D supplementation

- **The following groups should be advised to take vitamin D supplementation:**

- **The following groups should be advised to take vitamin D supplementation:**
 - ⇒ all pregnant and breastfeeding women should take a daily supplement containing 10 μ g of vitamin D
 - ⇒ all children aged 6 months - 5 years. Babies fed with formula milk do not need to take a supplement if they are taking more than 500ml of milk a day, as formula milk is fortified with vitamin D

- ⇒ adults > 65 years
- ⇒ Current NOS guidelines recommend that all people over the age of 65 take a daily supplement containing 10mcg (400 IU) of vitamin D.
- ⇒ people who are not exposed to much sun should also take a daily supplement

- **Testing for vitamin D deficiency:**

- ⇒ **Advised in the following situations (NOS guidelines)**
 - patients with bone diseases that may be improved with vitamin D treatment e.g. known osteomalacia or Paget's disease
 - patients with bone diseases, prior to specific treatment where correcting vitamin deficiency is appropriate e.g. prior to intravenous zoledronate or denosumab
 - patients with musculoskeletal symptoms that could be attributed to vitamin D deficiency e.g. bone pain ? osteomalacia
- ⇒ **Testing for vitamin D deficiency is not necessary in the following:**
 - Patients with osteoporosis → should always be given calcium/vitamin D supplements
 - People at higher risk of vitamin D deficiency → should be treated anyway

Phosphate

Phosphate overview

- **Normal range:** 3.0–4.5 mg/dL (1.0–1.5 mmol/L)
- **Daily phosphate requirement:** 1-2 g, but typical intake is higher, 3-6 g, mostly through meats and grains.
- **Foods that are rich in phosphate** include: **dairy products, (Cheddar cheese),** fibre rich foods, chocolate, and processed meats.
- **Absorption** occurs mainly in the jejunum
- **Storage**
 - ⇒ 85% of the body's phosphate is found in the bone matrix.
 - ⇒ Outside of bone, phosphate is mainly found in the intracellular space (esp. in soft tissue cells).
- **Importance**
 - ⇒ Component of many important molecules, including creatine phosphate, membrane phospholipids, DNA, ATP/ADP, 2,3-DPG, and NADP
- **Excretion**
 - ⇒ All circulating phosphate is not bound to proteins, so all of it can be filtered, and the kidney is the only way it is excreted.
 - ⇒ The **majority** (70%) of filtered phosphate is reabsorbed by **type 2a sodium phosphate cotransporters** located on the apical membrane of the renal **proximal tubule**. Impaired expression or function of these transporters is associated with nephrolithiasis.
 - ⇒ kidney failure leads to high serum phosphate levels (hyperphosphatemia) that can cause secondary bone fractures and bone pain (renal osteodystrophy).
- **Phosphate homeostasis**
 - ⇒ Vitamin D stimulates intestinal absorption and release of phosphate from bones.
 - ⇒ PTH stimulates renal phosphate excretion by inhibiting its reabsorption in the kidneys.

Hypophosphataemia

Definition

- serum phosphate level of less than 2.5 mg/dL (0.8 mmol/L).

Causes and Mechanisms: The 4 major mechanisms of hypophosphataemia are:

- Redistribution of extracellular phosphate into cells (Transcellular phosphate shifts)
 - ⇒ **hyperventilation** → respiratory alkalosis → activating phosphofructokinase → moves phosphate into cells → stimulates intracellular glycolysis.
 - ⇒ Glycolysis leads to phosphate consumption as phosphorylated glucose precursors are produced.
 - ⇒ Any cause of hyperventilation (eg, sepsis, **anxiety**, **pain**, heatstroke, alcohol withdrawal, diabetic ketoacidosis [**DKA**], hepatic encephalopathy, salicylate toxicity, neuroleptic malignant syndrome [NMS]) can precipitate hypophosphatemia.
- Decreased intestinal absorption
 - ⇒ chronic diarrhea
 - ⇒ malabsorption syndromes
 - ⇒ severe vomiting
 - ⇒ nasogastric (NG) tube suctioning
 - ⇒ Alcohol use disorder
- Increased urinary loss. (**the most common cause of hypophosphatemia**)
 - ⇒ primary and secondary hyperparathyroidism.
 - ⇒ Osmotic diuresis, such as seen in hyperosmolar hyperglycemic syndrome (HHS)
 - ⇒ Fanconi syndrome (proximal tubule dysfunction)
 - ⇒ X linked hypophosphataemic rickets
 - ⇒ Oncogenic hypophosphataemic osteomalacia
- Pseudohypophosphatemia
 - ⇒ Mannitol

What types of medications can impair gut phosphate absorption?

- Antacids, specifically those that are aluminium or magnesium based.**

Fanconi syndrome is a genetic disorder of the renal proximal tubule whereby various substances—including glucose, bicarbonate, potassium, and phosphate—are unable to be reabsorbed, causing their loss in the urine. It can lead to growth defects and bone disorders.

Features

- Cardiac:** arrhythmias
- Musculoskeletal:** Osteomalacia (fatigue, muscle pain and weakness, respiratory muscle weakness). **severe hypophosphatemia (< 2.5 mg/dL) is associated with elevated serum alkaline phosphatase.**
- Neurological:** paresthesia, altered mental state, seizures
- Hematological:** anemia, haemolysis, and thrombocytopenia
- Impaired immunity** (WBC and platelet dysfunction)
- Hypophosphatemia → ↓ 2,3-diphosphoglycerate (2,3-DPG), (a glycolytic intermediate in red blood cell metabolism that has higher affinity for deoxygenated hemoglobin than for

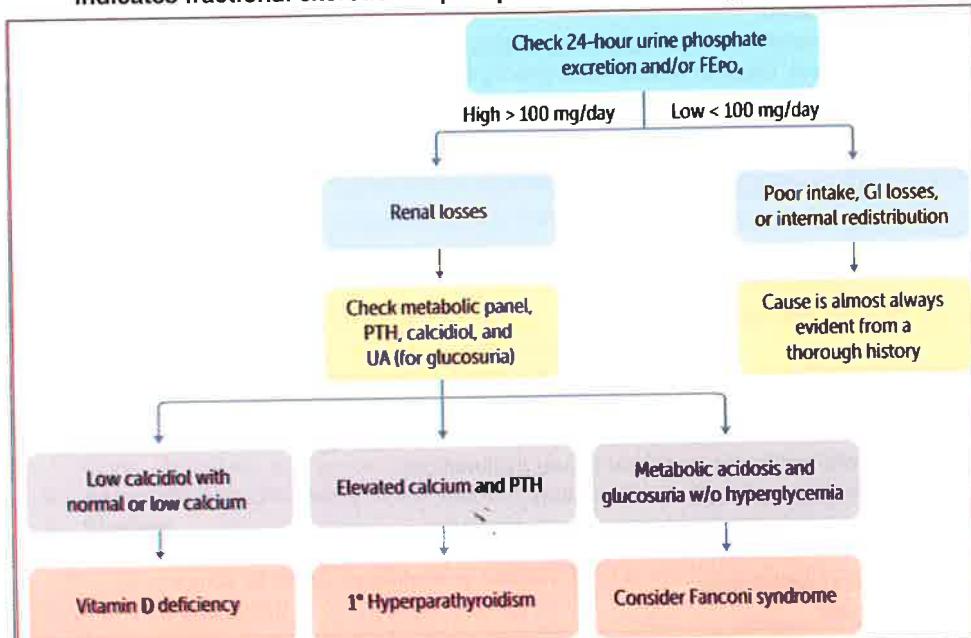
oxygentated hemoglobin) → ↑ affinity of hemoglobin (Hb) for oxygen → shifting the dissociation curve to the left → impairing red blood cell release of oxygen to tissues

Why is hypophosphatemia a problem in patients with respiratory failure?

- Limited release of oxygen to tissues because of 2,3-DPG depletion and respiratory muscle weakness.

Diagnosis and evaluation

- Summary of the clinical work-up for a patient with hypophosphatemia (FEPO₄ indicates fractional excretion of phosphate and UA, urinalysis).



MRCPUK- part-1-Sep 2017: what is the mechanism of Hypophosphataemia during treatment of DKA?

- Shift from extracellular to intracellular space

MRCPUK-part-1-Sep 2017: what is the mechanism of Hypophosphataemia in alcoholic patients after hospital admission ?

- Shift from extracellular to intracellular space. The alcoholic patient often has chronic phosphate depletion, and, after admission to the hospital, is prone to severe hypophosphatemia resulting from redistribution of extracellular phosphate into the cells.
 - Two factors may contribute to this shift:
 - I.V therapy with dextrose-containing solutions or refeeding → ↑Glucose → ↑ insulin release → ↑ phosphate uptake by the cells
 - alcohol withdrawal → hyperventilation → acute respiratory alkalosis → intracellular alkalosis → stimulates intracellular phosphofructokinase → ↑ glycolysis → movement of phosphate into cells.

Hyperphosphataemia

Causes and mechanisms

- Decreased phosphate excretion (Renal failure, Hypoparathyroidism)
- Increased tissue breakdown (e.g., tumor lysis syndrome, rhabdomyolysis, crush injury) → shifts intracellular phosphate to extracellular space
- Increased phosphate intake (e.g., phosphate-containing enemas)
- Pseudohypoparathyroidism
- Vitamin D intoxication
- Bisphosphonates (have also been shown to cause hypophosphatemia)
-

Features

- Often asymptomatic
- High PO₄³⁻ levels cause the formation of an insoluble compound with calcium, which can lead to:
 - ⇒ Hypocalcemia
 - ⇒ Nephrolithiasis
 - ⇒ Calcifications in the skin
- ↓ calcium + ↑ phosphate levels seen in:
 - ⇒ renal failure, hypoparathyroidism, and pseudohypoparathyroidism
- ↑ calcium + ↑ phosphate seen in:
 - ⇒ vitamin D intoxication (↓ PTH + ↑ vitamin D)
 - ⇒ milk-alkali syndrome (↓ PTH + ↓ vitamin D)

Management

- Treat the underlying cause.
- Discontinue phosphate intake (dietary or medication).
- Give phosphate binders (e.g., aluminium hydroxide, calcium carbonate).
- Consider dialysis (especially in severe cases of hyperphosphatemia in patients with renal failure).

Hyperparathyroidism

Classification

Type	PTH	Serum Ca	Serum Phos	Causes
Primary	Normal	High	low	parathyroid adenoma
Secondary	High	Normal or low	High	CRF → ↓ vit D → ↓ gut Ca ²⁺ absorption → ↓ Ca ²⁺ → ↑ PTH CRF → ↓ phosphate excretion → hyperphosphatemia. Causes of ↓ Ca²⁺: <ul style="list-style-type: none"> renal failure (most common) insufficient vit D, insufficient Ca²⁺ in the diet, excessive Mg²⁺ in the diet
Tertiary	High	High	High	hyperplasia of the glands, and loss of response to Ca ²⁺ . occurs after years of secondary hyperparathyroidism PTH is raised, calcium is raised and so is phosphate, whilst eGFR is significantly decreased

Primary hyperparathyroidism

Mechanism of PTH effects:

- Reabsorbs calcium at distal tubule
- Excretes phosphate at proximal tubule
 - ⇒ A mnemonic to remember this is PTH = "Phosphate Trashing Hormone."
- Activates vitamin D from 25 to the 1,25 dihydroxy form
 - ⇒ increased activity of renal **1-α-hydroxylase** (which converts inactive 25-hydroxycholecalciferol into active 1, 25-dihydroxycholecalciferol),
- Reabsorbs both calcium and phosphate from bone

In exams primary hyperparathyroidism is stereotypically seen in elderly females with an unquenchable thirst and an appropriately normal or raised parathyroid hormone level.

Pathophysiology

- PTH indirectly stimulates osteoclasts by binding to its receptor on osteoblasts, inducing RANK-L and M-CSF synthesis

Epidemiology

- the most common cause of hypercalcemia
- occurs in 0.1% of the population
- most commonly found in women between 50 and 60 years of age
- Two to three times more common in women than men.

Causes

- 80%: **solitary adenoma**
- 15%: hyperplasia
- 4%: multiple adenoma
- 1%: carcinoma (**PTH is grossly elevated**)

Pathophysiology: overproduction of Parathyroid hormone (PTH) by parathyroid chief cells

- **Effect of PTH on bone** → ↑ bone resorption → ↑ release of calcium phosphate → ↑ calcium levels
 - ⇒ Induces RANKL expression in osteoblasts → binding of RANKL to RANK on osteoclasts → activation of osteoclasts
 - ⇒ Induces IL-1 expression in osteoblasts → activation of osteoclasts
- **Effect of PTH on the kidneys** → ↑ phosphate excretion (phosphaturia)

Features: 'bones, stones, abdominal groans and psychic moans'

- **The majority of patients are asymptomatic.**
- **Cardiovascular system**
 - ⇒ Arterial hypertension → Left ventricular hypertrophy
 - ⇒ Shortened QT interval on the ECG
- **Kidney**
 - ⇒ Nephrolithiasis, nephrocalcinosis → abdominal/flank pain (**Stones**)
 - ⇒ Polyuria, polydipsia (**thrones**)
- **Musculoskeletal system (bones)**
 - ⇒ Bone, muscle, and joint pain
 - ⇒ Pseudogout
- **GIT (abdominal groans)**
 - ⇒ Nausea, constipation (↑ calcium → ↓ smooth muscle contraction → constipation)
 - ⇒ Gastric or duodenal ulcers

- ⇒ Acute pancreatitis
- **Psychological symptoms:** depression, fatigue, anxiety, sleep disorders (**psychiatric overtones**)

"Stones, bones, abdominal groans, thrones, and psychiatric overtones!"

Associations

- Hypertension
- Multiple endocrine neoplasia: MEN I and II
 - ⇒ **The association of primary hyperparathyroidism and a gastrinoma would suggest a diagnosis of multiple endocrine neoplasia type 1.**
- Osteitis fibrosa cystica
 - ⇒ The cystic bone spaces seen on radiography are most likely osteitis fibrosa cystica, a condition in which brown, fibrous tissue fills bone cysts.
 - ⇒ Consist of osteoclasts and hemosiderin (hemosiderin accumulates in bone cysts as a result of hemorrhage)
 - ⇒ Subperiosteal thinning

Investigations

- Raised calcium, low phosphate
 - ⇒ **Hypophosphataemia is due to → reduced renal reabsorption of phosphate.**
- PTH may be raised or normal (**A high or even normal PTH concentration in the presence of hypercalcaemia would support the diagnosis of hyperparathyroidism**)
- technetium-MIBI subtraction scan
- **Technetium (99mTc) sestamibi scanning**
 - ⇒ **The most sensitive and specific technique for tumor localization**
 - ⇒ Only performed prior to surgery to determine the exact location of the abnormal glands
- 24 hour urinary calcium may be useful if used in comparison to the serum calcium in order to distinguish familial hypocalciuric hypercalcaemia from primary hyperparathyroidism.
- Urinary cAMP increases, because PTH works on the G protein pathway, Gs, which uses cAMP as a secondary messenger.

The effect of PTH on calcium and phosphate

Mechanism	calcium	Phosphate
Excretion by kidneys	Low	High
Absorption from gut	High	High
Absorption from bone	High	High
Net Serum concentration	High	Low

The PTH level in primary hyperparathyroidism may be normal

Phosphate is usually elevated or normal in bone metastases (this clue could differentiate primary hyperparathyroidism from cancer metastases)

Treatment

- Surgery**

- ⇒ In cases of solitary adenoma: Only the respective gland is removed.
- ⇒ In cases of hyperplasia: All four glands are removed.

- Parathyroidectomy: Indications:**

- ⇒ **Symptomatic** patient (definitive signs and symptoms of hypercalcaemia- such as proximal weakness, gait disturbance, hyper-reflexia)

- ⇒ **Asymptomatic + one of the following:**

- **Age less than 50**
- Markedly elevated corrected serum calcium (**above 3 mmol/l**),
- Serum albumin-adjusted calcium **greater than 0.25 mmol/L above the normal range**
- 24 hour total urinary calcium excretion greater than **10 mmol** (400 mg)
- Renal stones, or presence of nephrocalcinosis on ultrasound or CT.
- Impaired renal function, **creatinine clearance reduced by 30% or more**
- Presence of osteoporosis or osteoporotic fracture (**Bone mineral density T-score less than -2.5 at any site**)
- Unwillingness of patient to follow advice of medical surveillance. (Patient request; adequate follow-up unlikely).

- Complication of parathyroidectomy : hungry bone syndrome**

- ⇒ **occur after parathyroidectomy if the hyperparathyroidism has been long standing.**
- ⇒ Characterized by severe **hypocalcemia** despite a normal or increased serum concentration of parathyroid hormone
- ⇒ Upon removal of the parathyroid adenoma the hormone levels fall rapidly (they have a very short half-life) and the osteoclast activity is subsequently diminished, and the bones rapidly begin re-mineralisation - 'hungry bone syndrome'.
- ⇒ In addition to hypocalcemia, patients can also develop hypophosphatemia, hypomagnesemia, and hyperkalemia.
- ⇒ **x-ray changes very similar to metastatic lytic lesions if left untreated.**



Bilateral hand radiographs in a middle-aged woman demonstrating generalised osteopenia, erosion of the terminal pharyngeal tufts (acro-osteolysis) and sub-periosteal resorption of bone particularly the radial aspects of the 2nd and 3rd middle phalanges. These changes are consistent with a diagnosis of hyperparathyroidism.

Secondary hyperparathyroidism

Secondary hyperparathyroidism (sHPT): Hypocalcemia results in reactive hyperplasia of the parathyroid glands, develops due to decreased levels of calcium in the blood (reactive HPT). → overproduction of PTH.

Definition

- Elevation of parathyroid hormone (PTH) in response to hypocalcemia induced by phosphate retention and reduced calcitriol synthesis as a consequence of reduced renal function
- Because 2° HPT is a compensatory mechanism of the parathyroid glands, it commonly resolves with normalization of calcium and phosphorus homeostasis (eg, renal transplantation).

Causes

- Chronic kidney disease (most frequent cause)
- Malnutrition
- Vitamin D deficiency (e.g., reduced exposure to sunlight, nutritional deficiency, liver cirrhosis)

Secondary hyperparathyroidism is due to the overproduction of PTH secondary to low calcium. Usually, this is seen in chronic renal failure or vitamin D deficiency.

Pathophysiology

- Secondary hyperparathyroidism: ↓ calcium and/or ↑ phosphate blood levels → reactive hyperplasia of the parathyroid glands → ↑ PTH secretion
- Chronic kidney disease → impaired renal phosphate excretion → ↑ phosphate blood levels → ↑ PTH secretion
- In addition, CKD → ↓ biosynthesis of active vitamin D → ↓ intestinal calcium resorption and ↓ renal calcium reabsorption → hypocalcemia → ↑ PTH secretion

Feature

- ↓ Ca^{2+} , ↑ serum phosphate, ↑ PTH
- ↑ alkaline phosphatase (renal osteodystrophy).

Management

- **Dietary phosphate restriction**
 - ⇒ In patients with chronic kidney disease (CKD), dietary phosphorus should be restricted to 800 to 1000 mg/day.
- **Calcium and vitamin D replacement**
- **Phosphate binders (sevelamer):** indicated when phosphorus levels are high. If phosphorus or PTH levels cannot be controlled despite dietary phosphorus restriction.
 - ⇒ **Mechanism of action:** binds phosphate in the gut (sevelamer is nonabsorbable) → ↓ phosphate absorption → ↓ serum phosphate → ↓ PTH
 - ⇒ **Indication:** hyperphosphatemia caused by chronic kidney disease
- **Calcimimetics (e.g., cinacalcet)**
 - ⇒ **Mechanism of action:** modulation of calcium-sensitive receptor (CaSR) in parathyroid glands → ↑ sensitivity of the receptor to circulating Ca^{2+} → inhibition of PTH release

⇒ **Indication**

- Primary hyperparathyroidism after failed parathyroidectomy
- Hypercalcemia in hemodialysis patients with secondary hyperparathyroidism due to CKD
- Parathyroid carcinoma with hypercalcemia
- Parathyroidectomy is reserved for severe secondary hyperparathyroidism resistant to medical management (on maximal doses of cinacalcet, and still, the PTH level is high).
 - ⇒ bone pain, fracture, or calciphylaxis.
- **Renal transplant is the optimal treatment for secondary HPT.**

Unlike primary hyperparathyroidism, secondary hyperparathyroidism is treated medically by correcting vitamin D deficiency.

Tertiary hyperparathyroidism

Epidemiology

- tertiary HPT requiring surgical intervention occurs in 1–5% of patients with HPT after undergoing kidney transplant.

Pathophysiology

- Chronic renal disease → longstanding secondary hyperparathyroidism → hyperplasia of all four glands → refractory and autonomous secretion of PTH (secrete PTH regardless of Ca²⁺ level) → **hypercalcemia**.

Causes

- Caused by persistent secondary HPT

Management

- treatment of patients with tertiary HPT is surgical.
- medical treatment is not curative and, generally, not indicated.
- **Cinacalcet** should be only offered in patients who are unfit for surgery.

Hypoparathyroidism

Causes

- **Postoperative:** most commonly occurs as the result of accidental injury to parathyroids (or their blood supply) during thyroidectomy, parathyroidectomy, or radical neck dissection
- **Autoimmune:** second most common cause
- **Infiltration of parathyroid gland:** (e.g. Wilson disease, hemochromatosis)
- **Radiation-induced destruction**
- Gram-negative sepsis
- Toxic shock syndrome
- HIV infection
- Congenital: Parathyroid gland aplasia or hypoplasia (DiGeorge syndrome)
- **Frequency increased in alcoholics, particularly in association with hypomagnesaemia.**
 - ⇒ Alcohol → Hypercalciuria & hypermagnesuria → hypocalcemia and

Features

- Symptoms of hypocalcemia, such as tetany (see hypocalcemia topic)
- Hypocalcemia with low or inappropriately normal PTH
- Hyperphosphatemia

Treatment

- Treat underlying disease
- Calcium and vitamin D supplementation
- Recombinant human PTH can reduce the amount of supplemental calcium and vitamin D required.

Pseudohypoparathyroidism

Definition

- end-organ (i.e., bones and kidneys) resistance to parathyroid hormone (PTH) despite sufficient PTH synthesis due to a defective Gs protein α subunit

Epidemiology

- Occurs twice as frequently in females as in males.

Inheritance

- Autosomal dominant
- Inherited from the mother (GNAS gene imprinting)

Pathophysiology

- mutations in GNAS1 → Defective Gs protein α subunit → missing activation of adenylate cyclase when PTH binds to Gs → resistance to PTH in kidney and bone tissue

Types

- type I: there is a complete receptor defect
- type II : the cell receptor is intact.

Features

- Albright hereditary osteodystrophy (AHO)
 - ⇒ Short stature, Round face
 - ⇒ Obesity
 - ⇒ Brachydactyly of the 4th and 5th fingers (**short fourth and fifth metacarpals**)
 - ⇒ Intellectual disability
 - ⇒ Subcutaneous calcification
- Symptoms related to low calcium and high phosphate levels: Seizures, Numbness, tetany, Cataracts, Dental problems

Diagnostics

- Persistent hypocalcemia despite ↑ PTH levels
- ↑ Phosphate levels
- Alkaline phosphatase: high

- Diagnosis is made by measuring urinary cAMP and phosphate levels following an infusion of PTH.
 - ⇒ In hypoparathyroidism this will cause an increase in both cAMP and phosphate levels.
 - ⇒ In pseudohypoparathyroidism type I neither cAMP nor phosphate levels are increased
 - ⇒ whilst in pseudohypoparathyroidism type II only cAMP rises.

Radiographic features

- Musculoskeletal manifestations**
 - ⇒ soft tissue calcification
 - ⇒ exostoses: short metaphyseal or more central and perpendicular to long axis of bone
 - ⇒ broad bones with coned epiphyses
- CNS / head and neck manifestations**
 - ⇒ basal ganglia calcification
 - ⇒ sclerochoroidal calcification
 - ⇒ deep white matter calcification

Management

- Calcium and vitamin D supplementation

Pseudo pseudohypoparathyroidism

- Similar phenotype to pseudohypoparathyroidism but **inherited from the father** and associated with **normal biochemistry (normal calcium, PTH, and phosphate)**

Pseudohypoparathyroidism is when the defect is inherited from the **mother** while **pseudo pseudohypoparathyroidism** is inherited from the **father**.

Osteomalacia

The symptoms of proximal bone pain with **hypocalcaemia** and **low phosphate** suggest a diagnosis of **osteomalacia**

↓↓ Ca ↓↓ P ↓ vit D + ↑↑ ALP → osteomalacia

Definition

- Defective mineralization of osteoid, most commonly due to vitamin D deficiency.
- Normal bony tissue but decreased mineral content.
- If occurred in children (growth plates have not fused) called rickets.

Pathophysiology

- ↓vitamin D →↓serum Ca²⁺ →↑PTH secretion →↓serum phosphate → impaired mineralization.
- Hyperactivity of osteoblasts →↑ALP.

Risk factors

- Lack of sun exposure, e.g. people who spend more time inside and people who are cover themselves up (so that cholesterol cannot be converted to vitamin D in the skin).
- Ethnic groups who are dark-skinned
- Asians who eat chapattis (as the phytic acid in the chapattis chelates vitamin D and calcium)

Causes

- Vitamin D deficiency e.g. malabsorption, lack of sunlight, diet
- Vitamin D resistant; inherited
- Renal failure
- Liver disease, e.g. cirrhosis
- Drug induced e.g. anticonvulsants
- **Mercury poisoning** or any heavy metal poisoning causes an acquired Fanconi syndrome with proximal (type 2) renal tubular acidosis.

Features

- Bone pain, particularly around the hips and lower back
- Pathologic fractures
- Muscle tenderness
- Proximal myopathy → Waddling gait and difficulty walking
- Symptoms of hypocalcemia

Investigation

- ↓ Calcium and ↓ phosphate
- ↑ Alkaline phosphatase and ↑ PTH
- X-ray:
 - ⇒ children - cupped, ragged metaphyseal surfaces → **Rickets**
 - ⇒ adults - **Looser zones (pseudofractures)**: transverse bands of radiolucency indicating defective calcification of osteoid (**Linear areas of low density**)

Differential diagnoses

- Malignancy
- Osteoporosis
- Paget disease of the bone

Treatment

- **Vitamin D deficiency:** administration of vitamin D
- **Defective vitamin D metabolism or vitamin D-independent forms:** treatment of underlying disease

May 2013 exam: A 58-year-old woman C/O aches and pains in her bones. Generally weak and lethargic. Low calcium, phosphate and vitamin D levels combined with a raised alkaline phosphatase and parathyroid hormone level. What is the most appropriate management?

→ Start vitamin D₃ supplementation (Δ → osteomalacia)

Osteopetrosis

Overview

- also known as marble bone disease
- rare disorder of **defective osteoclast function** resulting in failure of normal bone resorption
- results in dense, thick bones that are prone to fracture
- bone pains and neuropathies are common.
- calcium, phosphate and ALP are normal
- stem cell transplant and interferon-gamma have been used for treatment

Osteoporosis

In osteoporosis, there is **decreased bone mass**, but mineralization is normal.

Definition

- Loss of cortical bone mass which leads to bone weakness and increased susceptibility to fractures
- Bone mineral density (BMD) = (T-score equal to or less than -2.5).
- Normal bone mineralization and lab values (serum Ca²⁺ and PO₄).

Causes

- **Primary osteoporosis** (most common form)
 - ⇒ **Type I** (postmenopausal osteoporosis): postmenopausal women
 - Estrogen stimulates osteoblasts and inhibits osteoclasts.
 - ↓estrogen levels following menopause →↑bone resorption.
 - ⇒ **Type II** (senile osteoporosis): gradual loss of bone mass as patients age (especially > 70 years)
 - ⇒ **Idiopathic osteoporosis**
 - Idiopathic juvenile osteoporosis
 - Idiopathic osteoporosis in young adults
- **Secondary osteoporosis**
 - ⇒ Drug-induced/iatrogenic
 - Most commonly due to systemic long-term therapy with corticosteroids (e.g., in patients with autoimmune disease)
 - Anticonvulsants (e.g., phenytoin, carbamazepine)
 - L-thyroxine
 - Anticoagulants (e.g., heparin)
 - Proton pump inhibitors
 - glitazones
 - Aromatase inhibitors (e.g., anastrozole, letrozole): used for breast cancer in postmenopausal women, converts androgens into estrogens.
 - Immunosuppressants (e.g., cyclosporine, tacrolimus)
 - ⇒ Endocrine/metabolic: hypercortisolism, hypogonadism, hyperthyroidism, hyperparathyroidism, renal disease
 - ⇒ Multiple myeloma
 - ⇒ Excessive alcohol consumption
 - ⇒ Immobilization

Risk factors

- **female sex** : ♀ > ♂ (~ 4:1)
- **Advancing age**
- **Family history of osteoporotic fracture**
- **Low body mass index**
- History of glucocorticoid use
- Rheumatoid arthritis
- Current smoking
- Malabsorption (e.g. Coeliac's), malnutrition (e.g., a vegan diet low in calcium and vitamin D), anorexia
- Premature menopause (<45 years) (Early menarche and late menopause are associated with reduced risk of fracture)

Feature

- Asymptomatic (osteoporosis in the absence of fracture, **does not cause pain**).
- **Pathological fractures** that are caused by everyday-activities (e.g., bending over, sneezing) or minor trauma (e.g. falling from standing height)
 - ⇒ Common locations: vertebral (most common) > femoral neck > distal radius (Colles fracture) > other long bones (e.g., humerus)
 - ⇒ Vertebral compression fractures
 - Commonly asymptomatic but may cause acute back pain and possible point tenderness without neurological symptoms
 - Multiple fractures can lead to decreased height and thoracic kyphosis.

Diagnosis

- **DXA (dual-energy x-ray absorptiometry) scan**
 - ⇒ **Definition:** a noninvasive technique that calculates bone mineral density (BMD) by using two x-ray beams
 - ⇒ **Measurement sites:** femoral neck and lumbar spine (femoral neck is the preferred site because of its higher predictive value for fracture risk)
 - ⇒ **Indications**
 - General recommendation for women ≥ 65 years and men ≥ 70 years (one-time screening test)
 - In younger individuals, if additional risk factors are present: e.g., prolonged glucocorticoid use, low BMI (< 21 kg/m²), alcohol use, smoker, amenorrhea
 - ⇒ **Results:** T-score is defined as the difference in standard deviations between the patient's BMD and the BMD of a young adult female reference mean.
 - Osteoporosis: T-score ≤ -2.5 SD
 - Osteopenia: T-score of -1 to -2.5 SD
 - ⇒ **Repeating a DXA scan**
 - **DXA scans are of limited value in assessing response to treatment.**
 - **Review DXA 2-5 years from previous scan if it is likely to influence management**
- **Plain radiography**
 - ⇒ If osteoporosis is diagnosed: Radiographic assessment of the whole skeletal system is recommended, particularly if a fracture is already suspected or height loss has occurred.
 - ⇒ Increased radiolucency is detectable in cortical bones once 30–50% of bone mineral has been lost
 - ⇒ Osteoporosis can be diagnosed if vertebral compression fractures are present ; commonly an incidental finding because such fractures are typically asymptomatic

- Blood tests:** Normal serum calcium, phosphate, and parathyroid hormone (PTH) levels
- Investigations for secondary causes** (e.g. osteomalacia, myeloma)
- Assess the risk of subsequent fractures;**
 - fracture risk assessment tools (FRAX or Q Fracture)
 - The use of FRAX for fracture risk assessment is preferred

Osteoporosis diagnosis according to the WHO and International Osteoporosis Foundation criteria:

diagnosis	T score	definition
normal	(≥ -1)	hip BMD greater than the 1 SD below the young adult reference mean
osteopaenia	(-1 to -2.5)	hip BMD between 1 and 2.5 SD below the young adult reference mean
osteoporosis	(≤ -2.5)	hip BMD 2.5 SD or more below the young adult reference mean
Severe osteoporosis	(≤ -2.5 PLUS fracture)	hip BMD 2.5 SD or more below the young adult reference mean + one or more fragility fractures

Osteoporosis is diagnosed if T-score ≤ -2.5 SD and/or a fragility fracture is present.

Glucocorticoid-induced osteoporosis

Overview

- Steroids cause osteoporosis by:
 - bone resorption,
 - \downarrow calcium absorption from the gut,
 - \uparrow urinary calcium excretion,
- The dose?
 - \Rightarrow The risk $\uparrow\uparrow$ with prednisolone 7.5mg a day for 3 or more months.

Management of patients at risk of corticosteroid-induced osteoporosis

- The RCP guidelines divide patients into two groups.
 - \Rightarrow age > 65 years **or** H/O previously fragility fracture \rightarrow give bone protection.
 - Fragility fracture - defined by The WHO as resulting from a mechanical force equivalent to a fall from standing height or less which should not ordinarily cause a fracture.
 - \Rightarrow age < 65 years \rightarrow bone density scan

T score	Management
Greater than 0	Reassure
Between 0 and -1.5	Repeat bone density scan in 1-3 years
Less than -1.5	Offer bone protection

- The first-line treatment is alendronate and risedronate. Patients should also be calcium and vitamin D replete.
- National Osteoporosis Guideline Group (NOGG) 2017 (UK):

- ⇒ Women and men age ≥ 70 years with a previous fragility fracture or taking high doses of glucocorticoids (≥ 7.5 mg/day prednisolone), should be considered for **bone protective therapy**.
- ⇒ In other individuals fracture probability should be estimated using **FRAX**
 - Bone-protective treatment should be started at the onset of glucocorticoid therapy in individuals at high risk of fracture.

Osteoporosis: assessing fracture risk

Osteoporosis in a man - check testosterone

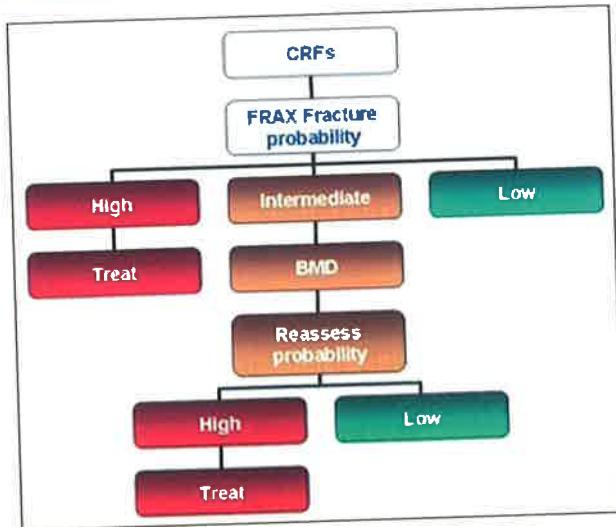
Who should be assessed for fragility fracture?

- All women aged ≥ 65 years and all men aged ≥ 75 years.
- Younger patients + presence of risk factors, such as:
 - ⇒ previous fragility fracture
 - ⇒ current use or frequent recent use of oral or systemic glucocorticoid
 - ⇒ history of falls
 - ⇒ family history of hip fracture
 - ⇒ other causes of secondary osteoporosis
 - ⇒ low body mass index (BMI) (< 18.5 kg/m)
 - ⇒ smoking
 - ⇒ alcohol (> 14 units/week for women and > 21 units/week for men).

Methods of risk assessment: NICE recommend using a clinical prediction tool such as FRAX or Q Fracture to **assess a patient's 10-year risk of developing a fracture**.

- **FRAX**

- ⇒ Estimates the 10-year risk of fragility fracture in patients with clinical risk factors (CRFs)
- ⇒ valid for patients aged 40-90 years (> 90 already considered at high risk.)
- ⇒ based on international data so use not limited to UK patients
- ⇒ assesses the 11 factors: age, sex, weight, height, previous fracture, parental fracture, current smoking, glucocorticoids, rheumatoid arthritis, secondary osteoporosis, alcohol intake.
- ⇒ NICE recommend arranging a DEXA scan if FRAX (without BMD) shows an intermediate result
- ⇒ **Interpreting the results of FRAX**
 - If the FRAX assessment was done **without a bone mineral density (BMD)** measurement
 - ❑ low risk: reassure and give lifestyle advice
 - ❑ intermediate risk: offer BMD test
 - ❑ high risk: offer bone protection treatment
 - If the FRAX assessment was done **with a bone mineral density (BMD)** measurement:
 - ❑ low risk: Reassure
 - ❑ intermediate risk: consider treatment
 - ❑ high risk: strongly recommend treatment



- **Q Fracture**

- estimates the 10-year risk of fragility fracture
- developed in 2009 based on UK primary care dataset
- can be used for patients aged 30-99 years (this is stated on the Q Fracture website, but other sources give a figure of 30-85 years)
- includes a larger group of risk factors e.g. cardiovascular disease, history of falls, chronic liver disease, rheumatoid arthritis, type 2 diabetes and tricyclic antidepressants
- **Interpreting the results of FRAX**

- Patients are not automatically categorised into low, intermediate or high risk. Instead the 'raw data' relating to the 10-year risk of any sustaining an osteoporotic fracture. This data then needs to be interpreted alongside either local or national guidelines, considering certain factors such as the patient's age.

- **DEXA scan**

- NICE recommend against routinely measure BMD (i.e. a DEXA scan) to assess fracture risk without prior assessment using FRAX (without a BMD value) or Q Fracture
- There are some situations where NICE recommend arranging DEXA scan directly to assess BMD rather than using one of the clinical prediction tools:
 - before starting treatments that may have a rapid adverse effect on bone density (e.g., sex hormone deprivation for treatment for breast or prostate cancer).
 - in people aged < 40 years who have a major risk factor, such as history of multiple fragility fracture, major osteoporotic fracture, or current or recent use of high-dose glucocorticoids (more than 7.5 mg prednisolone or equivalent per day for ≥ 3 months).

When should we reassess a patient's risk (i.e. repeat the FRAX/Q Fracture)?

- if the original calculated risk was in the region of the intervention threshold for a proposed treatment and only after a minimum of 2 years, or
- when there has been a change in the person's risk factors

Osteoporosis: management

Indications

- History of fragility fractures in postmenopausal women
 - ⇒ Age < 75 years + osteoporotic fragility fractures + confirmed osteoporosis (a T-score of -2.5 SD or below)
 - ⇒ Age ≥ 75 years + osteoporotic fragility fractures (a DEXA scan may not be required)
- T-scores ≤ -2.5
- T-score between -1 and -2.5 with severely increased risk of fracture

Bisphosphonates: e.g., alendronate, risedronate

- The drug of choice for osteoporosis
- Agents
 - ⇒ Oral bisphosphonates (alendronic acid, ibandronic acid and risedronate sodium)
 - recommended only if the 10-year probability of osteoporotic fragility fracture is at least **1%**.
 - ⇒ Intravenous bisphosphonates (ibandronic acid and zoledronic acid)
 - recommended only if the 10-year probability of osteoporotic fragility fracture is at least **10% OR 1% + difficulty of taking oral bisphosphonates** or these drugs are contraindicated or not tolerated.
- Mechanism of action: inhibition of osteoclasts → bone resorption (reduce the risk of both vertebral and non-vertebral fractures)
- First-line: alendronate
 - ⇒ around 25% of patients cannot tolerate alendronate, usually due to upper gastrointestinal problems.
- Second line (if alendronate not tolerated): risedronate or etidronate
- Instructions for administration
 - ⇒ Should be taken after an overnight fast and at least 30 minutes before the first food or drink (other than water) of the day or any other oral medicinal products or supplementation (including calcium).
 - ⇒ With plenty of water (e.g. 200 ml of water)
 - ⇒ Patients should not lie down for 30 minutes after taking the tablet.
- Side effects
 - ⇒ Hypocalcemia
 - ⇒ Esophagitis, esophageal cancer
 - ⇒ **Osteonecrosis of the jaw:** most common with intravenous **zoledronic acid**
- Contraindicated in patients with a GFR less than 35 ml/min
- Treatment review should be performed after 3 to 5 years
 - ⇒ Continuation of bisphosphonate treatment beyond 3-5 years can generally be recommended in: individuals age ≥75 years, those with a history of hip or vertebral fracture, those who sustain a fracture while on treatment, and those taking oral glucocorticoids.
- Treatment failure
 - ⇒ NICE defines an **unsatisfactory response to treatment** when a patient has another **fragility fracture** despite adhering fully to **treatment for longer than 1 year** and there is evidence of a **decline in BMD**.

Bisphosphonates should be taken at least 30 minutes before meals, with plenty of water, and the patient should maintain an upright position for at least 30 minutes following intake to prevent esophagitis.

Denosumab

- **Action**
 - ⇒ Human monoclonal antibody that **inhibits RANK ligand** on the surface of osteoclast precursors, which in turn **inhibits the maturation of osteoclasts** leads to reduced bone reabsorption.
- **Indication**
 - ⇒ High risk of fracture + **unable to take bisphosphonate** (intolerance or a contraindication)
 - ⇒ Indicated in **patients with impaired renal function** or in whom bisphosphonates therapy failed
- **Administration**
 - ⇒ given as a single subcutaneous injection **every 6 months**, therefore, tolerated by patients who don't want a daily subcutaneous injection
- **Side effects**
 - ⇒ Like bisphosphonates it is associated with **osteonecrosis of the jaw**, but **not other adverse events such as reflux oesophagitis**.
 - ⇒ The risk of a dynamic bone disease may be less for denosumab versus bisphosphonates because it does not accumulate in bone.

Teriparatide: parathyroid hormone analog

- **Mechanism of action:**
 - ⇒ **Increased osteoblast activity** (the main effect) → increased bone growth
 - ⇒ **increased calcium absorption from the gut and reduced calcium excretion from the kidney.**
- **Indication:**
 - ⇒ **Severe osteoporosis** (T-score ≤ -3.5) or for patients + **unable to take bisphosphonate (intolerance, contraindication or unsatisfactory response)**
 - age ≥ 65 years + T-score of ≤ -4.0 SD, **or**
 - age ≥ 65 years + T-score of ≤ -3.5 SD + more than two fractures, **or**
 - age 55–64 years + T-score of ≤ -4 SD + more than two fractures.
- **Advantages**
 - ⇒ Effective at reducing vertebral and non-vertebral fractures in post-menopausal women
 - ⇒ reduces both pain and disability due to spinal fractures. It is the most appropriate choice to control both the immediate symptoms and for long-term prevention.
- **Administration**
 - ⇒ administered once daily by subcutaneous injection and therefore, not preferred by many patients, who don't like injectables.
 - ⇒ the maximum total duration of treatment restricted to **18 months**.
- **Side effects**
 - ⇒ Hypercalcemia (usually transitory)
 - ⇒ Increased risk of osteosarcoma in patients with:
 - Paget disease of the bone (or an unexplained elevation of alkaline phosphatase)
 - Prior cancers or radiation therapy

- **Contraindications**

- ⇒ pre-existing hypercalcaemia,
- ⇒ severe renal impairment, (eGFR < 30 mL/minute/ 1.73 m²)
- ⇒ severe hepatic impairment,
- ⇒ metabolic bone diseases other than primary osteoporosis (including hyperparathyroidism and Paget's disease of bone)
- ⇒ unexplained elevations of alkaline phosphatase
- ⇒ previous radiation treatment to the skeleton.

Raloxifene - selective oestrogen receptor modulator (SERM)

- **Action**

- ⇒ act as a weak oestrogen-receptor agonists in some systems and as oestrogen antagonists in others.

- **Indication**

- ⇒ Secondary prevention of osteoporotic fragility fractures in postmenopausal women + contraindications to bisphosphonates or those who also require breast cancer prophylaxis.
- ⇒ In patients with breast cancer it should not be used for osteoporosis treatment or prevention until treatment of the breast cancer, including adjuvant treatment, has been completed.
- ⇒ Raloxifene is not recommended for the primary prevention of osteoporotic fragility fractures in postmenopausal women (NICE updated February 2018)

- **Advantage**

- ⇒ increase bone density in the spine and proximal femur
- ⇒ may decrease risk of breast cancer

- **Disadvantages**

- ⇒ reduce risk of vertebral fractures, but has not yet been shown to reduce the risk of non-vertebral fractures
- ⇒ less effective in preventing loss of bone mineral density versus bisphosphonates or denosumab.
- ⇒ may worsen menopausal symptoms
- ⇒ **increased risk of thromboembolic events**

- **Contraindications**

- ⇒ history of venous thromboembolism (VTE)
- ⇒ hepatic impairment, cholestasis
- ⇒ severe renal impairment
- ⇒ unexplained uterine bleeding or endometrial cancer

Strontium ranelate

- **Action**

- ⇒ 'Dual action bone agent' - increases deposition of new bone by osteoblasts (promotes differentiation of pre-osteoblast to osteoblast) and reduces the resorption of bone by **inhibiting osteoclasts**

- **Indication**

- ⇒ Severe osteoporosis in men and postmenopausal women at increased risk of fractures [when other treatments are contra-indicated or not tolerated]
- ⇒ the European Medicines Agency in 2014 said it should only be used by people for whom there are no other treatments for osteoporosis due to **increased risk of cardiovascular and thromboembolic events**

- **Administration**

- Administration
 - ⇒ The dose is 2 g once daily in water, preferably at bedtime.
 - ⇒ **Advice to avoid food for 2 hours before and after taking granules**, particularly calcium-containing products e.g. milk; also preferably avoid concomitant antacids containing aluminium and magnesium hydroxides for 2 hours after taking granules.

- **Contraindications**

- Contraindications
 - ⇒ Cerebrovascular disease
 - ⇒ Current or previous venous thromboembolic event
 - ⇒ Ischaemic heart disease
 - ⇒ Peripheral arterial disease
 - ⇒ Temporary or permanent immobilisation
 - ⇒ Uncontrolled hypertension.
 - ⇒ Severe renal impairment
 - ⇒ Should be discontinued during treatment with oral tetracycline or quinolone antibiotics.

Vitamin D and calcium supplementation

- Vitamin D and calcium supplementation should be offered to all women unless the clinician is confident, adequate calcium intake and are vitamin D replete
 - ⇒ **1500 mg/day of calcium and 400-800 pg /day of vitamin D**
 - ⇒ Dietary intake of calcium should be:
 - 800-1000 mg/day in childhood through early adulthood
 - 1000-1200 mg/day in the middle years
 - 1500 mg/day in the elderly

(SCE. Sample questions. Mrcpuk.org):

A **78-year-old** woman k/c/o osteoporosis presented with **acute mid-thoracic bone pain**. She had p/h/o right **wrist fracture**, **two previous episodes of vertebral fractures**. On **alendronate** acid and calcium and vitamin D tablets regularly for 3 years. DXA scan of spine (L2-L4): T score -3.8. What is the most appropriate treatment?

→ **teriparatide**

(SCE. Sample questions. Mrcpuk.org):

What cell type in bone primarily senses strain and microdamage?

→ **Osteocyte**

- Osteocytes derive from osteoblasts and have long cytoplasmic extensions, which detect strain in bone.

Pathophysiology of bone diseases:

- **Osteoporosis** → Decreased bone mass, but mineralization is normal.
- **Osteomalacia** → Decreased bone mineralization (due to vitamin D deficiency)
- **Paget's disease** → Disorder of bone remodeling (excessive bone resorption, followed by disorganized bone formation occurs, producing thickened but weak bone.)

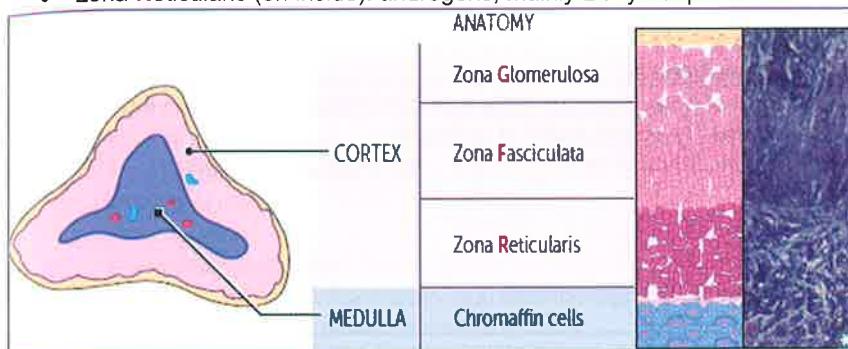
Adrenal gland conditions

Adrenal gland: Basics

Adrenal cortex mnemonic: GFR - ACD

Adrenal cortex (mnemonic GFR - ACD)

- zona **G**lomerulosa (on outside): mineralocorticoids, mainly **A**ldosterone
- zona **F**asciculata (middle): glucocorticoids, mainly **C**ortisol
- zona **R**eticularis (on inside): androgens, mainly **D**ehydroepiandrosterone (DHEA)



Adrenal medulla

- The adrenal medulla secretes
 - ⇒ **all the adrenaline in the body**
 - ⇒ Small amounts of noradrenaline.
- It essentially represents an enlarged and specialised sympathetic ganglion

Noradrenaline metabolism

- The action of noradrenaline released at sympathetic nerve endings is terminated by which mechanism?
 - ⇒ The majority are **re-uptaken by the axonal terminals** → into the neurosecretory granules
 - ⇒ Small amount is metabolised by monoamine oxidase (MAO)
 - ⇒ Smaller quantities that escape into the circulation are metabolised by catechol-O-methyl transferase (COMT)

Premature adrenarche

Definition and pathophysiology

- Premature maturation of the adrenal zona reticularis (adrenarche) → ↑androgen levels → **onset of pubarche before age 8 years in girls and age 9 years in boys.**

Associated conditions

- Associated with obesity, insulin resistance, and later development of PCOS and/or metabolic syndrome

Epidemiology

- **Most common cause of precocious pubarche**
- ♀ > ♂

Features

- Precocious pubarche: onset of pubic and/or axillary hair growth < 8 years in girls and < 9 years in boys
- Adult-type body odor
- Seborrhea, acne
- Increased height for age with a linear growth rate
- Other secondary sexual characteristics are absent (No breast development or testicular enlargement, or frank virilization.)

Diagnosis

- ↑ Serum androgen concentrations (DHEA-S, testosterone)
- Advanced bone age

Differential diagnosis

- Idiopathic premature pubarche**
 - ⇒ Premature onset of pubarche most likely due to increased sensitivity of the pilosebaceous units to normal levels of androgen
 - ⇒ No biochemical evidence of adrenarche (i.e., normal serum androgen concentrations)
 - ⇒ Normal bone age

Treatment

- No treatment is needed besides reassurance.

Premature puberty: signs of secondary sexual development occurring before the age of eight years in girls and the age of nine years in boys are considered premature and warrant careful evaluation.

Dehydroepiandrosterone sulphates (DHEAS)

Overview

- The most abundant circulating adrenal steroid.
- Hormone class:** Androgen
- Production site:** Zona reticularis of the adrenal cortex
- Function:** Substrate in estrogen and testosterone synthesis: DHEA → converted to estrogen and testosterone in peripheral tissue. Most of the DHEA is converted to androstenedione.
- Regulation of secretion:** CRH → ↑ secretion of ACTH in the pituitary gland → ↑ secretion of androgens in the adrenal cortex
- Decline with age

Clinical significance

- DHEAS is secreted exclusively by the adrenal glands and is therefore a good marker for adrenal androgen production.
- A mildly elevated DHEAS level is common in women with PCOS. In contrast, DHEAS values above 700 ng/dL (7 µg/ml, 18 µmol/L) are suggestive of adrenal neoplasm.
- Loss of functioning adrenal tissue as in Addison's disease may result in symptoms secondary to androgen deficiency, such as loss of libido.
- A trial of **dehydroepiandrosterone (DHEA)** is recommended in **women** with primary adrenal insufficiency who have low libido, low energy levels, or depressive symptoms despite glucocorticoid and mineralocorticoid replacement → **increasing a sense of wellbeing**

May 2008 exam: Addison's disease C/O a decrease in her libido. On examination there is a slight loss of pubic hair. What is the most likely cause? **Dehydroepiandrosterone (DHEA) deficiency**

Cortisol

Overview

- Hormone class: Glucocorticoids
- Production site: Zona fasciculata of the adrenal cortex
- Regulation of secretion: CRH → ↑ secretion of ACTH in the pituitary gland → ↑ secretion of glucocorticoids in the adrenal cortex
- Plasma cortisol levels in normal individuals show a circadian rhythm.
- **Levels are highest in the early morning and fall to their lowest levels during sleep at around midnight.**
- **At what time of day is a random cortisol test most likely to be abnormal?**
⇒ 2400 hours

Function

- **Metabolism:** Cortisol plays an important role in the mobilization of energy reserves.
 - ⇒ ↑ Gluconeogenesis to maintain blood glucose levels
 - ⇒ ↑ Glycogen synthesis to maintain glucose storage
 - ⇒ ↑ Protein catabolism
 - ⇒ ↑ Lipolysis
 - ⇒ ↑ Appetite
 - ⇒ ↑ Insulin resistance
- **Immune system:** anti-inflammatory and immunosuppressive effects (see "Pharmacodynamics of glucocorticoids")
- **Wound healing:** fibroblast inhibition → ↓ collagen synthesis → ↓ wound healing
- **Blood pressure:** mild mineralocorticoid effect (stimulation of aldosterone receptors in high concentrations) and ↑ potassium excretion → ↑ blood pressure

To remember the effects of cortisol, think "**A BIG FIB**": increased **A**ppetite, **B**lood pressure, **I**nsulin resistance, **G**lucose production, and decreased **FI**mmunity, and **B**one formation.

Cortisol levels are increased in:

- pregnancy
- conditions of physical and emotional stress
- oestrogens
- oral contraceptives
- amphetamines
- cortisone
- spironolactone.

What is the immediate precursor in the production of cortisol?

- **11-Deoxycortisol**

No need to evaluate cortisol secretion in critically ill patients

- In a critically ill patient CRH, ACTH and cortisol levels increase rapidly as a haemostatic response to the illness.
- acute illness → ↓ cortisol binding globulin and albumin → ↑ free cortisol levels (not truly reflective of adrenal hypersecretion)

Aldosterone

Overview

- Hormone class:** Aldosterone is the major circulating mineralocorticoid
- Production site:** zona glomerulosa of the adrenal cortex.

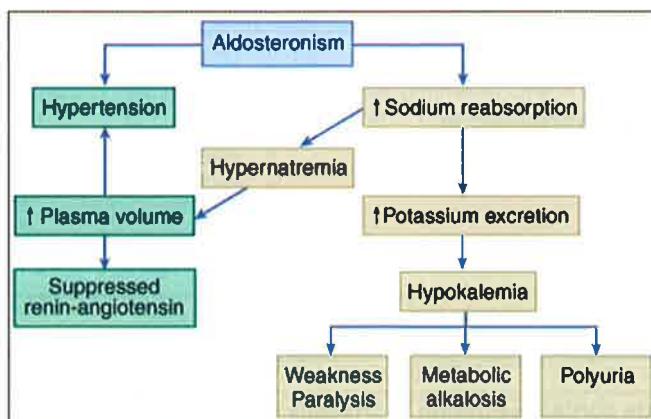
Action

- ↑ Na⁺ reabsorption → water reabsorption and K⁺ secretion into the urine → ↑ blood pressure, hypokalemia, and ↑ pH level.

Site of action: principal site: distal renal tubule

Regulation of synthesis and secretion:

- Stimulators**
 - ⇒ Hypovolemia → ↓ renal perfusion (e.g., due to hypotension, stimulation of β1 receptors in the kidney) → triggers renin release → promotes the conversion of angiotensinogen (produced in the liver) to angiotensin I (AT I), AT I is turned into angiotensin II via angiotensin-converting enzyme (highest concentration in the lungs where it is produced by vascular endothelial cells). Angiotensin II causes vasoconstriction and triggers the secretion of aldosterone.
 - ⇒ **Hyperkalemia**
- Inhibitors**
 - ⇒ Principle inhibitors
 - Hypervolemia
 - Hypokalemia
 - ⇒ Negative feedback: ↑ systemic arterial blood pressure → ANP release from atrial myocytes → inhibition of renin release → vasodilation, natriuresis, and ↑ diuresis



Adrenal hyperandrogenism

Causes

Primary adrenal diseases

- Premature adrenarche
- Adrenal tumors (adenomas, carcinomas, bilateral macronodular adrenal hyperplasia)

ACTH hypersecretion

- Congenital adrenal hyperplasia (CAH)
- ACTH-dependent Cushing's syndrome
- Glucocorticoid resistance
- Cortisone reductase deficiency

Hyperprolactinemia

Exogenous

- Androgens

Features

- Virilization: the appearance of male secondary sexual characteristics in a female individual
- Hirsutism: excessive male pattern hair growth (e.g., chin, upper lip, mid-sternum, abdomen, back, buttocks)
- Male-pattern hair loss
- Acne
- Increased muscle mass
- Voice deepening
- Clitoromegaly
- Rapid onset of virilization is suggestive of exogenous androgen intake or androgen-secreting tumors

Differential diagnosis of hyperandrogenism in females

Diagnosis	Characteristic finding
PCOS: Most common (75–80% of cases)	Polycystic ovaries on pelvic ultrasound
Nonclassic CAH	↑ 17-Hydroxyprogesterone
Congenital adrenal hyperplasia	Ambiguous genitalia
Cushing disease	↑ 24-hour urine free cortisol
Hypothyroidism	↑ TSH
Androgen-secreting tumor (e.g., Sertoli-Leydig cell tumor, adrenal)	↑ DHEA-S (> 700 µg/ dL)

Hyperaldosteronism: Overview

Definition: Increased secretion of aldosterone from adrenal gland.

Features and complications

- Hypertension
 - ⇒ ↑ Aldosterone → ↑ open Na⁺ channels in the cortical collecting ducts of the kidneys
 - ↑ Na⁺ reabsorption and retention → water retention → hypertension
- ↓ or normal K⁺
 - ⇒ may be normal in up to 50% of cases
 - ⇒ Diabetes insipidus: hypokalaemia → desensitization of renal tubules to antidiuretic hormone (ADH) → polyuria and polydipsia
- Metabolic alkalosis
 - ⇒ ↑ H⁺ secretion in the kidney in order to enable ↑ K⁺ reabsorption
- ↑ Aldosterone → reduce nitric oxide bioavailability → ↓ endothelium-dependent vasodilatation → ↑ risk of cardiovascular events.
- ↑ Aldosterone → ↑ collagen synthesis → promotes myocardial fibrosis and cardiac remodeling → ↑ myocardial stiffness and ↑ left ventricular mass → ↑ risk of ventricular arrhythmias and sudden cardiac death.
- 1° hyperaldosteronism does not directly cause edema due to aldosterone escape mechanism. However, certain 2° causes of hyperaldosteronism (eg, heart failure) impair the aldosterone escape mechanism, leading to worsening of edema.

Aldosterone escape

- Inappropriately elevated aldosterone → sodium and water retention → volume expansion → secretion of atrial natriuretic peptide (ANP) and pressure natriuresis → **compensatory diuresis** → “**escape**” from **edema formation and hypernatremia**
- In edematous disorders the aldosterone escape mechanism is impaired, resulting in worsening edema.

General causes of hyperaldosteronism

1. Primary hyperaldosteronism
 - ⇒ Due to **bilateral adrenal hyperplasia** (most commonly) and adrenal adenoma (Conn's syndrome) (less commonly)
 - ⇒ ↑ aldosterone → ↓ renin → ↑ aldosterone to renin ratio (ARR).
2. Secondary hyperaldosteronism
 - ⇒ Due to renovascular hypertension, **fibromuscular dysplasia**, juxtaglomerular cell tumors (renin-producing), and oedema (eg, cirrhosis, heart failure, nephrotic syndrome).
 - ⇒ The **raised aldosterone level is driven by raised renin levels**.
 - ⇒ ↓ blood flow to the kidneys (e.g. due to renal artery stenosis, heart failure, and cirrhosis). → ↓ renal perfusion → ↑ renin → ↑ aldosterone (aldosterone to renin ratio (ARR) will be normal).

Primary hyperaldosteronism

Bilateral idiopathic adrenal hyperplasia is the most common cause of primary hyperaldosteronism

Prevalence: 10–30% of all forms of hypertension

Causes

1. **The most common** → **Bilateral idiopathic adrenal hyperplasia (70%).**
2. Common → adrenal adenoma, termed Conn's syndrome.
3. Rare → Adrenal carcinoma
4. Glucocorticoid deficiency - also called glucocorticoid-remediable aldosteronism → high ACTH levels → increased aldosterone production.

Features

- Hypertension: May present with untreated or resistant hypertension
- Hypokalaemia, may leads to:
 - ⇒ fatigue, muscle weakness, cramping, headaches, and palpitations.
 - ⇒ polydipsia and polyuria from hypokalemia-induced nephrogenic diabetes insipidus.
 - ⇒ Abdominal distention (ileus from hypokalemia)
 - ⇒ seen in only 10-40% of patients
- Patient with **adrenal adenoma** do not have features of hyperandrogenaemia like hirsutism as benign adrenal tumours produce cortisol but not the androgens. **Absence of hirsutism and virilisation in a patient with other features of Cushing's syndrome favours adrenal adenoma** but needs further investigations.
- **Electrolytes:** Low/normal potassium. Normal/high sodium
- **ABG: Metabolic alkalosis**
 - ⇒ **Aldosterone act on renal distal convoluted tubule** → enhancing sodium reabsorption and potassium and hydrogen ion excretion → **Metabolic alkalosis**

Screening

- **Indications of primary aldosterone screening** (using aldosterone / renin ratio - after controlling for factors (including medicines) that may confound results):
 1. sustained HTN (>150/100 in 3 separate measurements taken on different days;
 2. HTN resistant to 3 antihypertensive drugs;
 3. HTN controlled with ≥ 4 medications;
 4. HTN + low potassium
 5. HTN + adrenal incidentaloma;
 6. HTN + sleep apnea;
 7. HTN + family history of early-onset hypertension or stroke before age 40;
 8. HTN + first-degree relatives of patients with primary aldosteronism.

Investigations

- **Screening test: Aldosterone-to-renin ratio (ARR)**
 - ⇒ ↑aldosterone and ↓renin (aldosterone-to-renin ratios are typically ≥ 20).
 - ⇒ used to screen for primary hyperaldosteronism and differentiate it from other causes of elevated aldosterone (e.g., secondary hyperaldosteronism).
- **Confirmatory testing if ARR screening test is positive** to verify that aldosterone production is nonsuppressible (i.e., not regulated by the RAAS).
 - ⇒ **Oral sodium loading test**

- Ensure high sodium intake for 3 days and collect 24-hour urine aldosterone on the last day.
- Primary hyperaldosteronism is highly likely if urinary aldosterone > 12 mcg/day.
- ⇒ **Saline infusion test**
 - Draw baseline laboratory studies (e.g., PRA, Plasma aldosterone), infuse normal saline over 4 hours, and draw laboratory studies again.
 - Primary hyperaldosteronism is very probable in patients with aldosterone levels > 10 ng/dL.
- ⇒ **Interpretation**
 - **Aldosterone suppression after interventions:** primary hyperaldosteronism unlikely. Consider other diagnoses.
 - **No aldosterone suppression after interventions:** primary hyperaldosteronism confirmed
- **Determine the underlying cause** (after confirmatory tests)
 - ⇒ **Adrenal CT**
 - Recommended as initial imaging modality after confirmatory tests (preferred over MRI)
 - excludes large tumors and helps differentiate possible surgical candidates (e.g., unilateral adenoma) from nonsurgical candidates (e.g., bilateral adrenal hyperplasia).
 - ⇒ **Adrenal venous sampling (AVS)**
 - AVS is the gold standard for biochemically **differentiating unilateral aldosterone overproduction from bilateral aldosterone overproduction.**
 - **Indications:** Both of the following criteria must be met.
 - ⇒ Adrenal CT suggestive of unilateral hyperaldosteronism
 - ⇒ Surgical intervention is desired and feasible
 - **Procedure:** catheterization of both adrenal veins and a peripheral vein (e.g., IVC) under fluoroscopy followed by a measurement of the aldosterone-to-cortisol ratio of each vein
 - **Findings**
 - ⇒ Unilateral disease: significant difference in the aldosterone-to-cortisol ratio between the right and left adrenal veins
 - ⇒ Bilateral disease: little to no difference in ratios between the two adrenal gland veins
 - ⇒ **Genetic testing**
 - for familial hyperaldosteronism type 1 (FH-I) (glucocorticoid remediable aldosteronism [GRA])
 - ⇒ In patients < 20 years
 - ⇒ in patients with a family history of PA or stroke at a young age (<40 years),
 - In very young patients, we suggest testing for germline mutations in *KCNJ5* causing familial hyperaldosteronism type 3 (FH-III).

Aldosterone-to-renin ratio (ARR): Approach

- **Eliminate confounding factors before testing**
 - ⇒ Correct hypokalemia (because low potassium suppresses aldosterone secretion)
 - ⇒ Encourage normal salt intake (do not restrict salt intake)
 - ⇒ Discontinue agents known to affect **ARR** and use an alternative agent.
 - Drugs need to be stopped: **ACEI, ARB, diuretics, and β-blockers** for 2 weeks (wash-out period) and **spironolactone** for 6 weeks.
 - alternative agent which can be used: **Alpha-blockers (e.g. doxazosin), calcium channel blockers (e.g. amlodipine) and Hydralazine**

- Although ACEi are associated with false negative test results, in clinical practice the ARR can be assessed without stopping these agents. In fact, ACEi may actually improve the sensitivity of the test.
- Alpha blockers such as doxazosin have the lowest effect on the renin-angiotensin system
- The blood sample should be taken in the morning during standing position (i.e. with the patient standing for 2 h)
 - ⇒ Values obtained in the upright position are more sensitive than supine test results.
 - ⇒ **aldosterone is usually higher when the patient is erect than when supine (in bilateral hyperplasia)**
- Positive screening tests
 - ⇒ Confirm diagnosis (e.g., oral sodium loading test or saline infusion test)
 - ⇒ Identify subtype and etiology (e.g., via imaging, adrenal venous sampling, and/or genetic testing)
- Negative screening tests
 - ⇒ Consider repeating screening tests if the likelihood of primary hyperaldosteronism remains high.
 - ⇒ Consider other causes of secondary hypertension.

Agents known to affect renin levels include aldosterone receptor antagonists, ACE inhibitors, and potassium-wasting diuretics. Alternatives include alpha blockers and hydralazine.

The effect of drugs on Aldosterone-to-renin ratio (ARR)

- Drugs with no effect on ARR
 - ⇒ Alpha-blockers
 - ⇒ Calcium channel blockers
 - ⇒ Hydralazine
- Drugs result in false negative
 - ⇒ ACE inhibitors & ARBs → ↑ renin & ↓ aldosterone
 - ⇒ Diuretics → ↑ both renin & aldosterone
- Drugs result in false positive
 - ⇒ Beta-blockers & Methyldopa → ↓ renin

Differential diagnosis

- Hypertension is also a feature of Liddle syndrome and steroid 11β-hydroxylase deficiency, **but aldosterone concentrations are low**.
- Secondary hyperaldosteronism:
 - ⇒ ↑renin → ↑aldosterone secretion (**plasma renin activity is normal or increased**).
- Adrenal hyperplasia can be differentiated from adrenal adenoma by measuring aldosterone levels on awakening, and 2-4 hours later while standing:
 - ⇒ **In adenoma, aldosterone levels decline on standing 2-4 hours later.**
 - ⇒ **in hyperplasia, levels increase.**

Management

- Adrenal adenoma: surgery
 - ⇒ Surgery is the treatment of choice for Conn's adenoma and leads to resolution of hypertension in around 70% of patients.
 - ⇒ **Aldosterone inhibition with spironolactone will bring the greatest additional reduction in blood pressure.**
- Bilateral adrenocortical hyperplasia: aldosterone antagonist e.g. **spironolactone**

Prognosis

- After removal of the adenoma the blood pressure is normal in 70% of patients at 1 year;
- 50% of patients are still normotensive after 5 years.

Bilateral hyperplasia vs adrenal adenoma

bilateral hyperplasia	adrenal adenoma
idiopathic adrenal hyperplasia (IAH)	Aldosterone-producing adenomas (APAs)
Commonest	common
higher prevalence in African Americans, persons of African origin, and, potentially, other blacks.	have more severe hypertension, hypokalemia, and higher urinary aldosterone than IAH.
4 times more prevalent in men than in women	more common in women than in men, with a female-to-male ratio of 2:1.
peaking in the sixth decade of life	The typical patient with an APA is a woman aged 30-50 years.
renin-angiotensin system (RAS)-mediated increase in aldosterone level occurs with upright posture.	decrease in the aldosterone level with upright posture
Loss of normal circadian rhythm of aldosterone secretion (normally: lowest around midnight, and highest in early morning)	preserved of normal circadian rhythm of aldosterone secretion

aldosterone-producing adrenal adenomas are commoner in young women, whereas bilateral adrenal hyperplasia tends to occur later and is commoner in men.

Aldosterone receptor antagonists

Agents: spironolactone, eplerenone

Action

- acts on the distal renal tubules as a competitive antagonist of aldosterone increasing sodium and water excretion and reducing potassium excretion (acts as a potassium-sparing diuretic)
- K+ enters cells in exchange for H+ → amplifies acidosis
- onset of action: requiring 2 or 3 days for maximum effect

Indications

- Hypertension (especially if hypokalemia is also present)
- Ascites/oedema due to congestive heart failure, nephrotic syndrome, or cirrhosis of the liver (mainly spironolactone)
- Hyperaldosteronism (PCOS)
- Nephrogenic diabetes insipidus (amiloride)
- Hypokalemia
- Hyperandrogenic states, e.g., polycystic ovary syndrome (spironolactone)

- Imaging features suggestive of malignancy: Mass diameter >4cm, **high density** (>20 HU).
- ⇒ If the adrenal mass is **indeterminate** on noncontrast CT and the results of the **hormonal work-up do not indicate significant hormone excess**, three options should be considered by a multidisciplinary team:
 - immediate additional imaging with another modality, there is little added benefit of MRI over CT in the examination of the adrenals
 - interval imaging in 6–12months (noncontrast CT)
 - ⇒ If the lesion enlarges by more than 20% (in addition to at least a 5mm increase in maximum diameter) during this period → surgical resection
 - ⇒ If the lesion enlarges by less than 20% → additional imaging after 6–12months should be performed.
 - Surgery without further delay.
- **Exclude functional hormonal secretion**
 - ⇒ **Exclude pheochromocytoma** by measurement of **plasma-free metanephrenines (most sensitive and specific screening test)** or alternatively **urinary fractionated metanephrenines** (less specific)
 - **The most important thing to exclude**, as catastrophic consequences can occur following anaesthesia or surgical intervention.
 - ⇒ Exclude cortisol excess by 1mg overnight dexamethasone suppression test
 - post dexamethasone serum cortisol levels $\leq 50 \text{ nmol/L} (\leq 1.8 \mu\text{g/dL})$ **exclude** autonomous cortisol secretion
 - ⇒ Exclude primary aldosteronism aldosterone/renin ratio

Treatment

- Surgery for functional secreting adenoma or suspicious features on imaging
- Observation and monitoring for asymptomatic, **nonfunctioning** unilateral **adrenal mass** and **benign features** on imaging.

The criteria for **surgical removal** of an adrenal tumour is a diameter of **4cm or more** as the risk of primary carcinoma with such size is of the order of 1 in 30.

Congenital adrenal hyperplasia (CAH)

CAH due to 11-beta hydroxylase deficiency can cause apparent mineralocorticoid excess syndrome (AMES) resulting in hypertension and hypokalemia

Which of the following is the best investigation to monitor a patient with classic salt wasting congenital adrenal hyperplasia (CAH)?

⇒ **17 hydroxyprogesterone (17 OHP) levels.**

Overview

- Autosomal recessive disorder
- **Associated with HLA B47**
- Affects males and females in equal numbers

- Non-classic congenital adrenal hyperplasia is a cause of hyperandrogenism in up to 1 in 1000 females, particularly those of Hispanic, Yugoslavian or Eastern European **Jewish descent**.

Pathophysiology

- CAH is caused by autosomal recessive defects in enzymes that are responsible for the production of cortisol.
- There are three subtypes of CAH:
 - ⇒ 21 β -hydroxylase deficiency (~ 95% of CAH)
 - ⇒ 11 β -hydroxylase deficiency (~ 5% of CAH)
 - ⇒ 17 α -hydroxylase deficiency (rare)
- Low levels of cortisol** → lack of negative feedback to the pituitary → **increased ACTH** → **adrenal hyperplasia** and increased synthesis of adrenal precursor steroids
- Non-classical forms result from milder enzyme dysfunction and therefore manifest later in life (adolescence or adulthood).

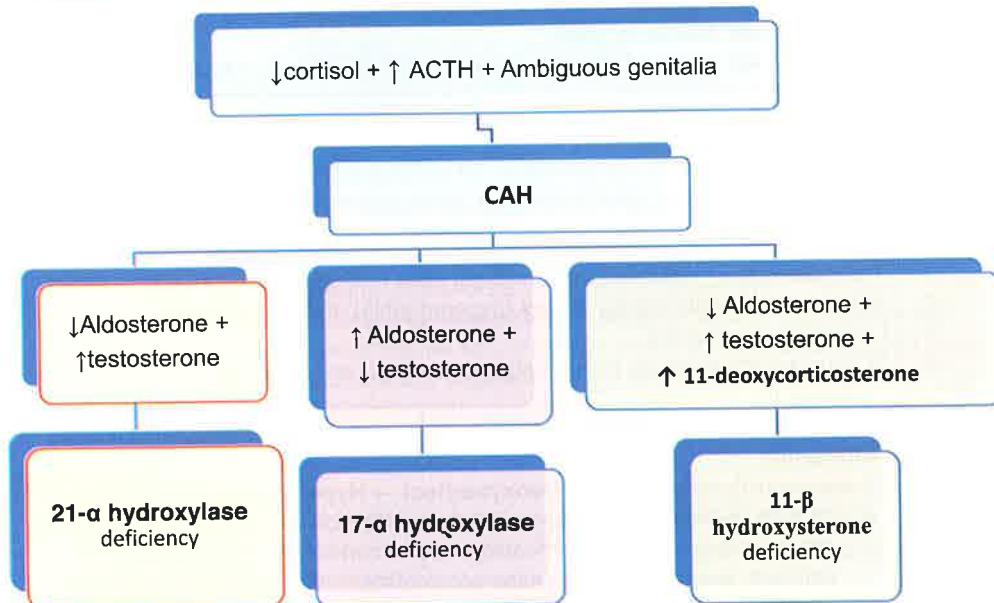
Types

- 21-hydroxylase deficiency (90%) most common cause**
 - ⇒ due to mutation of the CYP21A2 gene **on chromosome 6**
 - ⇒ ↑ **Testosterone** → virilisation of female genitalia and precocious puberty in males
 - ⇒ ↓ Aldosterone → **salt-losing crises** (hyponatremia) and hyperkalemia
 - ⇒ ↓ 11-deoxycorticosterone
 - ⇒ ↑ **17 hydroxy-progesterone** (commonly used as a screening test)
- 11-beta hydroxylase deficiency (5%)**
 - ⇒ ↑ **Testosterone** → virilisation of female genitalia and precocious puberty in males
 - ⇒ ↓ Aldosterone
 - ⇒ ↑ **11-deoxycorticosterone, 11-Deoxycortisol** → **Hypertension** and hypokalaemia
 - 11 Beta-hydroxylase is responsible for conversion of 11-deoxycorticosterone and 11-deoxycortisol to corticosterone and cortisol. As this enzyme is deficient, levels of these steroids accumulate.
 - **11-deoxycorticosterone** has **aldosterone-like activity**, and in high levels, it causes hypertension and hypokalaemia and **inhibits the production of renin** and consequently aldosterone.
 - ⇒ Mild elevation of 17-OH steroids (not as great as that seen with 21-hydroxylase deficiency), occasionally an incorrect diagnosis of 21-hydroxylase deficiency may however be made.
- 17-hydroxylase deficiency (very rare)**
 - ⇒ **17-hydroxylase** converts progesterone to 17- α -hydroxyprogesterone, which subsequently is converted to androsterenedione, testosterone, and finally estradiol.
 - ↓ Estradiol → ↓ menstrual cycle and ↓ secondary sexual characteristics.
 - Progesterone accumulates and is pushed into the aldosterone synthesis pathway → hypertension and hypokalemia
 - ⇒ ↑ **Aldosterone** → **hypertension and hypokalemia**
 - ⇒ ↓ **Testosterone** → amenorrhea, no secondary sexual characteristics in females (non-virilising). Inter-sex in boys
 - ⇒ ↑ **11-deoxycorticosterone**

patients with 11 β -hydroxylase deficiency will present with increased blood pressure, hypokalemia and increased androgen levels, differentiating it from 17 α -hydroxylase deficiency.

A female born with virilisation but has **elevated blood pressure** likely has a deficiency in **11 beta-hydroxylase**.

- All 3 types of CAH cause → ↓ cortisol + ↑ ACTH
- 11-deoxycorticosterone **decreased only** in the 21-hydroxylase deficiency (increased in other 2 types)
- Testosterone **decreased only** in the 17-hydroxylase deficiency (increased in other 2 types)



Feature

Type	XX (female) genotype	XY (male) genotype
21 β -hydroxylase deficiency	<ul style="list-style-type: none"> Hypotension Clitoromegaly and/or male external genitalia along with a uterus and ovaries Precocious puberty Virilization, irregular menstrual cycles, infertility 	<ul style="list-style-type: none"> Hypotension Normal male external genitalia at birth Precocious puberty
11 β -hydroxylase deficiency	<ul style="list-style-type: none"> Hypertension Clitoromegaly and/or male external genitalia along with a uterus and ovaries Precocious puberty Virilization, irregular menstrual cycles, infertility 	<ul style="list-style-type: none"> Hypertension Normal male external genitalia at birth Precocious puberty
17 α -hydroxylase deficiency	<ul style="list-style-type: none"> Hypertension Normal female external genitalia at birth Delayed puberty (primary amenorrhea) or sexual infantilism 	<ul style="list-style-type: none"> Hypertension Female external genitalia with a blind-ending vagina and intra-abdominal testes at birth Delayed puberty or sexual infantilism

Classical CAH (C-CAH)	Nonclassical CAH (NC-CAH)
<ul style="list-style-type: none"> The sever form Less common Early onset (during the neonatal period or early infancy) Females present with ambiguous genitalia. Salt-wasting type (~ 67% of all classic forms) → "adrenal crises": vomiting and shock. Non-salt-wasting type (simple virilizing, ~ 33% of all classic forms) → No signs of shock. Males present with precocious puberty at age 2–4. 	<ul style="list-style-type: none"> The milder form more common Late onset (manifests during late childhood, adolescence, or adulthood) Normal external genitalia Symptoms of hyperandrogenism include hirsutism, acne, menstrual irregularity, androgenic alopecia, and impaired fertility

- ACTH excess → hyperpigmentation (common feature in all forms of CAH)
- Under- and over-treatment of CAH → Premature epiphyseal closure → short stature
- Patients might complain of no other symptoms apart from primary amenorrhoea.
- The clinical presentation may be indistinguishable from polycystic ovarian syndrome, with hirsutism being a dominant feature.

Type	21 β -hydroxylase deficiency	11 β -hydroxylase deficiency	17 α -hydroxylase deficiency
Blood pressure	Hypotension	Hypertension	Hypertension
Acid-base disorders	Metabolic acidosis	Metabolic alkalosis	Metabolic alkalosis
17-Hydroxyprogesterone	Elevated	Elevated	Decreased
11-Deoxycorticosterone	Decreased	Elevated	Elevated
Corticosterone	Decreased	Decreased	Elevated
Potassium	Elevated	Decreased	Decreased

Diagnosis

- Screening is conducted by measuring 17-hydroxyprogesterone → elevated
 - ⇒ can help to distinguish between PCOS and non-classical CAH.
- ACTH stimulation test (synacthen stimulation test)
 - ⇒ can diagnose 21-OH deficiency when the plasma 17-OH progesterone are more than 30 nmol/L.
 - ⇒ In individuals with borderline 17-hydroxyprogesterone levels, we recommend obtaining a complete adrenocortical profile after a cosyntropin stimulation test
- Genotyping
 - ⇒ only indicated when:
 - results of the adrenocortical profile after a cosyntropin stimulation test are equivocal, or
 - cosyntropin stimulation cannot be accurately performed (i.e., patient receiving glucocorticoid), or
 - for purposes of genetic counseling.
- Normal ultrasound scan will rule out other causes of primary amenorrhoea (Turner syndrome and testicular feminization).

Management

- Glucocorticoid replacement
 - ⇒ Hydrocortisone in neonates and children
 - ⇒ Prednisolone or dexamethasone in adolescents and adults
 - ⇒ steroids given in reverse circadian rhythm, i.e. a higher dosage at night and a lower dose in the morning (when steroids are given in higher doses at night → ACTH is suppressed → ↓ over-secretion of adrenal androgens and ↓ the normal physiological steroid peak in the morning)
- Symptomatic
 - ⇒ If the main concern is infertility, ovulation induction is the treatment of choice.
 - ⇒ If hirsutism is the presenting problem, then anti-androgens (such as flutamide) should be used.

- Restoring functional anatomy by surgery

- minimally virilized girls: surgical options, include delayed surgery and/ or observation until the child is older
- In severely virilized females (single urogenital opening) → early surgery to repair the urogenital sinus

- Specific treatment

- ⇒ **21 β -hydroxylase deficiency**

- Lifelong fludrocortisone therapy (aldosterone substitution)
- Sodium chloride (salt) supplements, especially during infancy and childhood

- ⇒ **11 β -hydroxylase deficiency**

- Spironolactone to block mineralocorticoid receptors
- Reduced dietary sodium intake

- ⇒ **17 α -hydroxylase deficiency**

- Spironolactone to block mineralocorticoid receptors
- Estrogen replacement therapy for female genotype; may be started in early puberty
- Reduced dietary sodium intake

- ⇒ **Salt-wasting CAH**

- Fluid resuscitation with intravenous normal saline
- Intravenous dextrose in patients with significant hypoglycemia
- Immediate administration of glucocorticoid replacement therapy

- ⇒ **Nonclassic CAH**

- Women: combined oral contraceptives are first-line treatment (alternatively glucocorticoid therapy)
- Men: usually no treatment required

Monitoring of treatment

- Efficacy of treatment is best monitored by 17-OH progesterone and androstenedione levels**
- Renin activity levels can be used to monitor the adequacy of mineralocorticoid and sodium replacement.

The dose of glucocorticoids must be increased during severe infection, critical illness, and perioperatively to meet increased demands to prevent adrenal crisis.

Glucocorticoid remediable aldosteronism (GRA)

GRA should be suspected as the cause of primary aldosteronism when there is a **positive family history** and the onset of **hypertension is before age 21 years**.

Overview

- GRA is a rare subtype of primary aldosteronism, also called familial hyperaldosteronism (FH) type I
- **Autosomal dominant** mutation leads to ACTH responsive aldosterone production from the zona fasciculata rather than the zona glomerulosa.
- It occurs because the regulatory portion of the 11b-OH gene binds to the aldosterone synthase gene.
- usually associated with bilateral adrenal hyperplasia.

Features

- **Strong family history** of early **resistant hypertension** and haemorrhagic strokes is characteristic.
- **Elevated plasma aldosterone and suppressed renin**
- **Hypokalaemia**
 - ⇒ **potassium is normal in more than one-half of cases** of GRA in contrast to the hypokalaemia frequently seen in primary aldosteronism.
- Markedly increased levels of **18-oxocortisol** and **18-hydroxycortisol**.
- **Responsive to corticosteroid therapy.**

Complications

- increased risk ruptured intracranial aneurysms → hemorrhagic stroke (higher than that reported in autosomal dominant polycystic kidney disease.)

Diagnosis

- dexamethasone suppression test
- genetic testing (now preferred over dexamethasone suppression testing for making the diagnosis of GRA)

Treatment

- physiologic doses of a glucocorticoid will correct the overproduction of aldosterone by suppressing ACTH.

The main clinical **clues suggesting GRA** in the normokalaemic, hypertensive patient are:

1. family history of hypertension
2. onset at a young age
3. frequent development of marked hypokalemia after the administration of a thiazide diuretic (which increases sodium delivery to the aldosterone-sensitive potassium secretory site in the cortical collecting tubule).

The combination of low renin, high aldosterone and raised urinary oxocortisol suggests glucocorticoid remediable aldosteronism (GRA).

GRA is autosomal dominant, and therefore genetic testing is the most appropriate investigation. (SCE-question samples-mrcpuk.org)

Pseudohyperaldosteronism

Definition

- Pseudohyperaldosteronism is characterized by a clinical picture of hyperaldosteronism with suppression of plasma renin activity and aldosterone.

Feature

- Hypertension
- Salt retention
- Hypokalaemia
- Low renin and aldosterone concentrations

Causes

- Congenital adrenal hyperplasia
- Exogenous mineralocorticoid
- Cushing syndrome
- Liddle syndrome
- 11β -hydroxysteroid dehydrogenase deficiency
- Glucocorticoid resistance
- Excessive **licorice** ingestion: Excessive consumption of licorice can lead to inhibition of cortisol degradation → hypertension associated with hypokalemia.

Syndrome of Apparent Mineralocorticoid Excess (SAME)

Definition

- AME** is a rare form of pseudohyperaldosteronism characterized by very early-onset and severe hypertension, associated with low renin levels and hypoaldosteronism.

Causes

- Congenital deficiency of **11-beta-hydroxysteroid dehydrogenase type 2** (11-beta-HSD2) : **Autosomal recessive** mutation.
- Acquired reduction of the activity of the **(11 bHSD)** enzyme caused by:
 - carbenoxolone
 - grapefruit juice
 - ↑ **liquorice** consumption (glycyrrhetic acid): black substance produced from the root of a plant used in medicine and sweets)

Pathophysiology

- With normal 11- beta-hydroxysteroid dehydrogenase type 2** (11-beta-HSD2) activity: 11-beta-HSD2 converts cortisol into cortisone (cortisone, unlike cortisol, does not activate mineralocorticoid receptors).
- With 11-beta-HSD2 deficiency (or inhibition):** ↓ cortisol conversion to cortisone → ↑ cortisol → ↑ mineralocorticoid receptor activity.

Feature

- Hypertension
- Low birth weight
- Failure to thrive
- Muscle weakness
- Polyuria and polydipsia due to nephrogenic diabetes insipidus
- Renal failure
- ↑ **Ratio of free urinary cortisol (urinary tetrahydrocortisol) to free urinary cortisone.** (AME patients create less cortisone)

In Syndrome of Apparent Mineralocorticoid Excess, cortisol has the **SAME** action as aldosterone.

Differential diagnosis

- differentiate between AME and Liddle's Syndrome by administering a potassium-sparing diuretic:
 - ⇒ Liddle's syndrome: **only** respond to a diuretic that binds the ENaC channel,
 - ⇒ AME: respond to a diuretic that binds to ENaC or mineralcorticoid receptor.

Treatment

- Cessation of licorice ingestion
- Spironolactone to decrease the mineralocorticoid effects
- Thiazide in hypercalciuria or nephrocalcinosis
- Corticosteroids: exogenous corticoids block ACTH and suppress the endogenous secretion of cortisol.

Spironolactone (an aldosterone receptor antagonist) is effective in treating the syndrome of apparent mineralocorticoid excess but not Liddle syndrome!

Phaeochromocytoma

Phaeochromocytoma: do 24 hr urinary metanephrenes, not catecholamines

Phaeochromocytoma - give Phenoxylbenzamine before beta-blockers

The 5 P's of pheochromocytoma:

- Pressure (BP)
- Pain (headache)
- Perspiration
- Palpitations
- Pallor/diaphoresis

Pheochromocytoma rule of 10's:

- 10% extra-adrenal
- 10% bilateral
- 10% malignant
- 10% occur in children
- 10% familial

Pheochromocytoma = Episodic hypertension

Pheochromocytoma is part of MEN II.

Definition

- Phaeochromocytoma is a rare tumors arising from chromaffin cells of the adrenal medulla and secreting catecholamines.

- ⇒ **Chromaffin cells** are modified post-ganglionic sympathetic cells that release catecholamines after stimulation by pre-ganglionic sympathetics.

Overview

- The majority of pheochromocytomas are benign, unilateral, catecholamine-producing tumors.
- Tumors arise from **chromaffin cells**, which are derived from the neural crest.
- Present in up to 1% of all hypertensive patients
- The peak incidence is between ages 20 to 40.
- Equal sex distribution
- familial in 10%
- bilateral in 10%
- malignant in 10%
- **Localisation**
 - ⇒ ~ 90% adrenal medulla (physiologically activated by acetylcholine)
 - ⇒ ~ 10% extra-adrenal in the sympathetic ganglia (most common site = organ of Zuckerkandl, adjacent to the bifurcation of the aorta)
 - ⇒ ~ 10% at multiple locations
- 25% of pheochromocytomas are hereditary (germline mutations):
 - ⇒ Multiple endocrine neoplasia type 2 (MEN 2A, MEN 2B)
 - ⇒ Neurofibromatosis type 1 (NF1)
 - ⇒ Von Hippel-Lindau disease (VHL)

Features

- **Episodic hypertension** (around 90% of cases, may be sustained)
 - ⇒ Triggers for paroxysmal elevations in blood pressure: foods and beverages high in tyramine (e.g., red wine, aged cheese), surgery, pressure on the tumor (e.g., during massage), or certain drugs (e.g., beta blockers, MAOIs)
- **Paroxysmal**
 - ⇒ Throbbing **headache** (80%) **the most common presenting feature**
 - ⇒ Diaphoresis (60%)
 - ⇒ Palpitations, tachycardia (70%)
 - ⇒ Pallor
 - ⇒ Abdominal pain and nausea
 - ⇒ Anxiety
- **Weight loss** due to increased basal metabolism
- **Hyperglycemia**
- **Signs of polycythemia, if EPO is secreted**
- **Other features consistent with associated familial disorders:**
 - ⇒ **MEN 2A**: medullary thyroid cancer, pheochromocytoma, and parathyroid hyperplasia
 - ⇒ **MEN 2B**: medullary thyroid cancer, pheochromocytoma, oral/intestinal neuromas, and marfanoid habitus
 - ⇒ **NF1**: cutaneous neurofibromas, cafe-au-lait spots, and Lisch nodules
 - ⇒ **VHL**: renal cell carcinoma, hemangioblastoma, angiomyomatosis, and pheochromocytoma

5 most important Problems (**5 P's**) of Pheochromocytoma: increased blood Pressure, head Pain (headache), Perspiration, Palpitations, and Pallor

Hypertensive crises can be triggered by palpation of the tumor on abdominal exam.

Investigations

- **Plasma free metanephrenes test**
 - ⇒ The best initial test
 - ⇒ The most sensitive test
- **24 hr urinary collection of metanephrenes**
 - ⇒ The most specific test (sensitivity 86%)
 - ⇒ False positive urinary metanephrenes can occur as a result of:
 - hypoglycaemia, stress, exercise, drugs such as methyldopa, dopamine agonists or ganglion-blocking antihypertensives, various foodstuffs including coffee, chocolate, bananas and citrus fruits.
 - ⇒ The presence of noradrenaline alone usually indicates an extra-adrenal tumour.
 - Paragangliomas (exception—organ of Zuckerkandl) secrete noradrenaline only, as they lack PNMT. Phenylethanolamine-N-methyltransferase (PNMT) is necessary for methylation of noradrenaline to adrenaline and is cortisol-dependent.
 - ⇒ Small adrenal tumours tend to produce more adrenaline whereas larger adrenal tumours produce more noradrenaline
 - ⇒ Tricyclic antidepressants and labetalol interfere with adrenaline measurements and should be stopped for 4 days
 - ⇒ Plasma and urinary methoxytyramine levels are indicators of malignancy and can show isolated increases in patients with 'biochemically negative' malignant
- **Clonidine suppression tests**
 - ⇒ may be used to differentiate patients who have borderline catecholamine levels
 - ⇒ Clonidine 300 micrograms orally—failure of suppression of plasma catecholamines into the normal range at 120 and 180min is suggestive of a tumour
- **Genetic testing:** if MEN2A, MEN2B, NF1, or VHL is suspected
- **Immunohistochemical staining:** positive for chromogranin, synaptophysin, and NSE
- **Adrenal/abdominal CT or MRI** (after positive biochemistry tests to localize tumor)
 - ⇒ The definitive methods for localisation
 - ⇒ MRI: unlike most other adrenal tumours, demonstrates a distinctive 'bright white' signal on T2-weighted MRI.
- **Meta-iodo-benzyl guanidine (MIBG) scanning**
 - ⇒ demonstrates specific uptake in sites of sympathetic activity
 - ⇒ used in cases where a tumour is confirmed biochemically but cannot be identified on CT or MRI.
 - ⇒ Performed preoperatively to exclude multiple tumours.
 - ⇒ Phenoxybenzamine may lead to false -ve MIBG imaging, so these scans should be performed before commencing this drug where possible.
- **18F fluorodopamine PET scanning** is superior to MIBG in localizing metastatic disease.



The image reveals a large left suprarenal mass. The appearances are typical of which, unlike most other adrenal tumours, demonstrates a distinctive 'bright white' signal on T2-weighted MRI.

Management

- **Initial management** → The patient must be first stabilized with medical management:
 - ⇒ **Alpha-blocker** (e.g. phenoxybenzamine), should be **given first, before a beta-blocker**.
 - ⇒ **beta-blocker** (e.g. propranolol): Unopposed beta blockade should not be used in the management of phaeochromocytoma because of the **risk of paradoxical increases in blood pressure**
- **Laparoscopic tumor resection (adrenalectomy): treatment of choice**
 - ⇒ No-touch technique
 - ⇒ Open surgical resection is reserved for large or invasive tumors.
 - ⇒ **Preoperative blood pressure management: combined alpha-adrenergic and beta-adrenergic blockade**
 - First, a non-selective irreversible alpha-blocker is given : **Phenoxybenzamine** blocks alpha-1 and alpha-2 adrenoceptors equally and irreversibly
 - After sufficient alpha-adrenergic blockade, a beta-blocker may be started for additional blood pressure control and control of tachyarrhythmias.

Prognosis

- benign phaeochromocytoma → The 5-year survival rate is 95%
- malignant phaeochromocytoma → The 5-year survival rate is 40%
- Hypertension may persist in 25% patients who have undergone successful tumour removal.
- SHB gene mutation patients are associated with a shorter survival.

Primary hypoadrenalinism (Addison's disease)

Addison's disease is associated with metabolic acidosis

Primary hypoadrenalinism is diagnosed by a short synacthen test and a failure to increase cortisol levels to above 500nmol/L

Pathophysiology

- Damage to the adrenal gland leads to the deficiency in all three hormones produced by the adrenal cortex: androgen, cortisol, and aldosterone. Clinical findings are noted after 90% of the adrenal cortex has been destroyed.
- Hypoaldosteronism → hypotension (hypotonic hyponatremia and volume contraction), hyperkalemia, metabolic acidosis
- Hypoandrogenism → Loss of libido + Impaired spermatogenesis (in men)
- Hypocortisolism leads to:
 - ⇒ ↑ ACTH → ↑ production of POMC (in order to increase ACTH production) → ↑ melanocyte-stimulating hormone (MSH) → hyperpigmentation of the skin (bronze skin)
 - ⇒ ↑ ADH level → retention of free water → dilutional hyponatremia
 - ⇒ ↓ Expression of enzymes involved in gluconeogenesis → ↓ rate of gluconeogenesis → hypoglycemia
 - ⇒ Lack of potentiation of catecholamines action → hypotension

Prevalence

- Prevalence is around 5 per 100,000.
- There is a female: male preponderance of 2:1

Causes

- **Autoimmune destruction of the adrenal glands**
 - ⇒ the commonest cause of hypoadrenalinism in developed countries (80% of cases)
 - ⇒ 70% of patients have circulating anti-adrenal antibodies.
- Associated with other autoimmune conditions such as
 - ⇒ pernicious anaemia
 - ⇒ thyroid disease
 - ⇒ Type 1 diabetes
 - ⇒ Vitiligo
 - ⇒ Chronic active hepatitis.
- **Infectious** (e.g. mycobacterial, fungal, HIV)
 - ⇒ Adrenal tuberculosis (15% of cases)
 - the most common cause in developing countries.
 - In case with high ESR, TB adrenalitis should be considered
 - the best investigation → CT abdomen
 - reversible with anti-tuberculosis medications if given at an early stage
 - ⇒ HIV: affect 10% of patients with HIV, due to cytomegalovirus (CMV)
 - ⇒ Fungal: Histoplasmosis: A systemic fungal infection caused by Histoplasma
 - ⇒ **Acute meningococcal sepsis due to *Neisseria meningitidis*** → disseminated intravascular coagulation (DIC) → acute adrenal hemorrhage, also known as **Waterhouse-Friderichsen syndrome**.
 - *Neisseria meningitidis* is a gram-negative diplococcus that grows on chocolate agar.
 - **purpuric rash** classically appears on the trunk and extremities secondary to the DIC
- **Infiltration** of the adrenal glands
 - ⇒ Tumors (adrenocortical tumors, lymphomas, metastatic carcinoma)
 - ⇒ Amyloidosis
 - ⇒ Hemochromatosis
- **Vascular** (e.g. hemorrhage, emboli, thrombus)

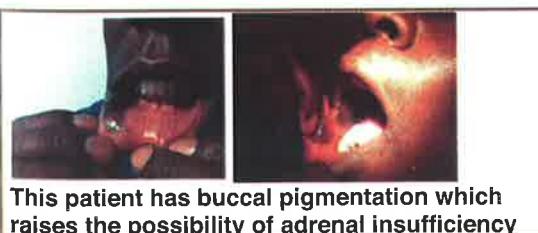
- ⇒ **Anti-phospholipid syndrome (Hughes' syndrome)** → haemorrhage through adrenal vein thrombosis → adrenal infarction
- ⇒ Anticoagulant overdose → bilateral hemorrhage in the adrenal glands → acute adrenal insufficiency. Flank pain, **hypotension refractory to resuscitative efforts**, and hypoglycemia indicate acute adrenal insufficiency due to heparin overdose.
- ⇒ Traumatic, iatrogenic (eg, surgery)
- **Drugs-induced adrenal insufficiency** → Cortisol synthesis inhibitors
 - ⇒ Antifungals: Ketoconazole, Fluconazole
 - ⇒ Antibiotics: Rifampin
 - ⇒ Antiepileptics: Phenytoin, Barbiturates

Thinning of pubic and axillary hair is seen in females with Addison's disease due to reduced production of testosterone from the adrenal gland

Most cases of adrenal insufficiency are subclinical and only become apparent during periods of stress (e.g., surgery, trauma, infections), when the cortisol requirement is higher!

Features

Hormonal changes	Clinical features	Laboratory findings
Hypoaldosteronism	<ul style="list-style-type: none"> • Hypotension • Salt craving 	<ul style="list-style-type: none"> • Hyponatremia • Hyperkalemia • Normal anion gap metabolic acidosis
Hypocortisolism	<ul style="list-style-type: none"> • Gastrointestinal complaints (e.g., nausea, vomiting, diarrhea) • Weight loss, anorexia • Fatigue, lethargy, depression • Muscle aches • Weakness • Sugar cravings • Orthostatic hypotension 	<ul style="list-style-type: none"> • Hypoglycaemia • Hyponatremia
Hypoandrogenism	<ul style="list-style-type: none"> • Loss of libido • Loss of axillary and pubic hair 	↓ DHEA-S
Elevated ACTH	<ul style="list-style-type: none"> • Hyperpigmentation of areas that are not normally exposed to sunlight (e.g., palmar creases, mucous membrane of the oral cavity) → pathognomonic 	↑ Melanocyte stimulating hormone (MSH))



This patient has buccal pigmentation which raises the possibility of adrenal insufficiency

Investigations

short Synacthen test is definitive diagnostic test

- **Routine laboratory studies**
 - ⇒ AGB → **Normal anion gap metabolic acidosis** due to ↓ bicarbonate
 - ⇒ CBC → normocytic normochromic anaemia, eosinophilia, lymphocytosis
 - ⇒ Electrolytes → Na ↓, K ↑, Ca ↑
 - ⇒ Blood glucose → Hypoglycemia
- **Endocrine studies:** Use stepwise endocrine testing
 - ⇒ **Morning cortisol level: initial test**
 - the diagnosis can be ruled out by a basal serum cortisol value in the upper end of the reference range or higher
 - ☞ cortisol > 500 nmol/l makes Addison's very unlikely
 - ☞ < 100 nmol/l strongly suggest hypocortisolism.
 - ☞ 100-500 nmol/l should prompt ACTH stimulation test to be performed
 - Random cortisol levels are of limited value, as cortisol secretion varies diurnally and with physiological stress.
 - Cortisol levels are influenced by cortisol-binding globulin (CBG) and albumin levels.
 - ⇒ **Morning ACTH level:** obtain if morning cortisol is low
 - Primary adrenal insufficiency: elevated ACTH levels > 100 pg/mL
 - Secondary/tertiary adrenal insufficiency: ACTH levels low to normal
 - ACTH secretion is subject to diurnal variation, which is why a morning sample is desirable.
 - Exogenous glucocorticoids (via any route) can suppress ACTH secretion through negative feedback.
 - ⇒ **Standard-dose ACTH stimulation test (short Synacthen test, cosyntropin test): gold standard test** to confirm the diagnosis of primary adrenal insufficiency
 - **Method**
 - ☞ Administration of 250 mcg exogenous ACTH to stimulate cortisol secretion
 - ☞ Measurement of cortisol levels before and 30 and 60 minutes after injection
 - ☞ Physiological response: exogenous ACTH → ↑ cortisol
 - ☞ If a patient is on prednisone, prednisolone, or dexamethasone, temporarily switch them to hydrocortisone and hold hydrocortisone 24 hours prior to testing.
 - **Interpretation**
 - ☞ In primary adrenal insufficiency: peak cortisol level < 18–20 µg/dL (< 500–550 nmol/L): **no rise in cortisol level**
 - ☞ In secondary/tertiary adrenal insufficiency: usually a rise in cortisol > 18–20 µg/dL (> 500–550 nmol/L)
 - **Variant:** low-dose (1 mcg) ACTH stimulation test
 - ☞ Uses a smaller dose of exogenous ACTH and is thought to better mimic physiological conditions
 - ☞ Studies show mixed results regarding its superiority to the standard-dose test.

- **Adrenal autoantibodies:** anti-21-hydroxylase: present in approximately **80%** of cases.

- **Imaging**

- ⇒ CXR: Screen for tuberculosis if an infective cause is suspected.
- ⇒ CT or MRI adrenal glands: Screen for adrenal hemorrhage and malignant or infiltrative disease.

Primary hypoadrenalinism

- **hyperprolactinaemia** is reported and is glucocorticoid-responsive.
- **High plasma renin and angiotensin II.**
- **High ACTH**
- **High lipotropin**
- **High plasma vasopressin**

Management

- Replacement therapy:
 - ⇒ **Glucocorticoid** → oral hydrocortisone.
 - Usually given in 2 or 3 divided doses. Patients typically require 20-30 mg per day, with the majority given in the morning dose
 - Medications and food interacting with hydrocortisone and cortisone acetate:
 - Drugs that affect hydrocortisone metabolism: need to **increase** the dose:
 - ❖ Anti-epilepsy/barbiturates, Antituberculosis
 - Drugs that affect hydrocortisone metabolism: need to **decrease** the dose:
 - ❖ Grapefruit juice, Liquorice
 - ⇒ **Mineralocorticoid** → fludrocortisone
 - Drugs that affect fludrocortisone (need to be avoided): Diuretics, Acetazolamide, Carbenoxolone, liquorice, NSAIDS
 - Drugs that affect fludrocortisone (need to increase the dose): Drosperone-containing contraceptive
 - Essential hypertension in a patient with PAI should be treated by adding a vasodilator, not by stopping the mineralocorticoid replacement, although a dose reduction should be considered.
- **Patient education**
 - ⇒ **During travelling**
 - Patient's with Addison's should be given a hydrocortisone injection kit when travelling to use it if unable to take oral hydrocortisone or vomiting. This can prevent Addisonian crisis
 - ⇒ **During an intercurrent illness**
 - **the glucocorticoid dose should be doubled**
 - If unable to take the normal oral hydrocortisone then the patient should be advised to take IM hydrocortisone to avoid adrenal crisis . This is why all patients with Addison's disease should have IM hydrocortisone for these situations.
 - ⇒ **During shift work**
 - Patients who work night-time shifts will need to adjust their dose schedule according to the work pattern (e.g. 10 mg upon awakening before going to work, instead of taking the first dose at 07:00 h). **doses should be taken from when waking**
 - ❖ Glucocorticoid therapy should ideally mimic endogenous cortisol rhythm with the lowest level at time of falling asleep and highest at waking.

- ❖ When a patient shifts their daytime routine, such as working on night shifts or travelling, the patient should be advised to take their morning dose on waking and maintain the timing from there.

⇒ **During an event of increased activity:**

- **If significantly strenuous activity** (e.g. marathon)
 - ❖ **double the dose of glucocorticoid and mineralocorticoids**
 - ❖ Mineralocorticoid therapy will be eventually required in adrenal insufficiency to counter intravascular volume depletion. It is important in the presence of increased fluid loss that the mineralocorticoid dose is adjusted. This is why doubling of the dose is advised.
 - ❖ If the patient was just on hydrocortisone then no additional fludrocortisone would be needed.
- **If less strenuous activity** (such as a long hike, was planned)
 - ❖ increasing the dose of hydrocortisone by 5-10mg would be reasonable, without any change in fludrocortisone. This change would also apply for any day that increased activity is planned for.

⇒ **During pregnancy:**

- **The doses of neither of the medications (hydrocortisone and fludrocortisone) should be preemptively increased in the first trimester.**

- A trial of **dehydroepiandrosterone (DHEA)** is recommended in **women** with primary adrenal insufficiency who have **low libido, low energy** levels, or **depressive** symptoms despite glucocorticoid and mineralocorticoid replacement.

Waterhouse-Frederickson syndrome

- adrenal failure due to bleeding into the adrenal glands (otherwise referred to as haemorrhagic adrenalitis) and is most commonly caused by meningococcal septicaemia.

A person with Addisons' who vomits should take **IM hydrocortisone until**

May 2008 exam: Addison's disease C/O a decrease in her libido. On examination there is a slight loss of pubic hair. What is the most likely cause? **Dehydroepiandrosterone (DHEA) deficiency**

Wolman's syndrome is characterised by:

1. primary adrenal failure,
2. hepatosplenomegaly, and
3. steatorrhoea.

Addisonian crisis

Signs/symptoms of Addisonian crisis

Neurological	Haemodynamic	Biochemical
<ul style="list-style-type: none"> • syncope • confusion • lethargy • convulsions 	<ul style="list-style-type: none"> • hypotension • hypothermia 	<ul style="list-style-type: none"> • hyponatraemia • hyperkalaemia • hypoglycaemia,

Management of Addisonian crisis (medical emergency)

- Intravenous fluids
 - ⇒ 1 litre normal saline infused over 30-60 mins or with dextrose if hypoglycaemic
- I.V Corticosteroids
 - ⇒ In a patient without a previous diagnosis of adrenal insufficiency → IV **dexamethasone**, as this will not interfere with cortisol assays needed for a short synacthen test, unlike hydrocortisone.
 - ⇒ For patients with a previously known diagnosis of adrenal insufficiency → 100 mg IV hydrocortisone because diagnostic testing is not necessary. continue hydrocortisone 6 hourly until the patient is stable.
 - ⇒ Mineralocorticoid (fludrocortisone) administration is not necessary in the acute setting because high cortisol exerts weak mineralocorticoid action.

Secondary hypoadrenalism

long Synacthen test can be used to distinguish primary adrenal failure from secondary adrenal failure

Definition

- Adrenal hypofunction due to a lack of adrenocorticotrophic hormone (ACTH)

Pathophysiology

- ↓ ACTH → hypoandrogenism and hypocortisolism
- **Aldosterone synthesis is not affected** (mineralocorticoid production is controlled by RAAS and angiotensin II, not by ACTH).
- If ↓ ACTH induced by ↓ CRH, then it is called tertiary adrenal insufficiency (↓ CRH → ↓ ACTH).

Causes

- **Hypopituitarism:** ↓ ACTH → ↓ endogenous cortisol
 - ⇒ Pituitary tumors
 - ⇒ Craniopharyngioma (in youngers)
 - ⇒ Irradiation
- **Conditions that decrease CRH production (tertiary adrenal insufficiency):** ↓ CRH → ↓ ACTH → ↓ cortisol release
 - ⇒ The most common cause is sudden discontinuation of chronic glucocorticoid therapy (e.g., infection, trauma, surgery) during prolonged glucocorticoid therapy
 - ⇒ Rarer causes include hypothalamic dysfunction (e.g., due to trauma, mass, haemorrhage, or anorexia).

Secondary and tertiary adrenal insufficiency are far more common than primary adrenal insufficiency

Feature

- Symptoms and signs are similar to those of Addison disease
- **Differentiating features** include:
 - ⇒ **Absence of hyperpigmentation** because ACTH secretion is not increased.
 - ⇒ **Absence of mineralocorticoid deficiency** (Aldosterone synthesis is not affected)
 - No dehydration or hypotension

- Relatively normal electrolyte. Hyponatremia if it occurs, is due to increased vasopressin secretion → volume expansion → dilutional hyponatremia. Hyperkalemia is not present
- ⇒ **Associated features of underlying cause**, e.g. visual field defects if pituitary tumour.
- ⇒ **Other endocrine deficiencies** may manifest due to panhypopituitarism (\downarrow thyroid and gonadal function and hypoglycemia). Adrenal crisis is likely if a patient is treated with thyroxine, without hydrocortisone replacement.
- ⇒ **Hypoglycemia is more common** in secondary adrenal insufficiency.

Primary adrenal insufficiency → Pigments the skin.

Secondary adrenal insufficiency → Spares the skin.

Tertiary adrenal insufficiency is due to → Treatment (cortisol).

Diagnosis

Confirmatory Serum Testing for Secondary Adrenal Insufficiency	
Test	Result
ACTH	Low (< 5 pg/mL)
Cortisol	Low (< 5 µg/dL [138 nmol/L])
ACTH stimulation test (short Synacthen test)	Normal or subnormal
Prolonged (24-h) ACTH stimulation test (Long Synacthen test)	Cortisol should continue to rise for 24 h

- **Long Synacthen test** (prolonged ACTH stimulation test for 24 h)

⇒ **Aim:**

- To diagnose secondary (or tertiary, ie, hypothalamic) adrenal insufficiency.

⇒ **Before the test:**

- **The simple short test is usually done initially**, because a **normal** response obviates the need for further investigation.
- If short Synacthen test is subnormal (failure to respond to ACTH → \downarrow cortisol) **and** secondary adrenal insufficiency is suspected → do long Synacthen test
- **Because pituitary failure may cause adrenal atrophy and hence failure to respond to ACTH**, the patient may need to be primed with **long-acting ACTH 1 mg IM once/day for 3 days** before the ACTH stimulation test if pituitary disease is suspected.

⇒ **Method:**

- Cosyntropin 1 mg IM is given, and cortisol is measured at intervals for 24 h, typically at 1, 6, 12, and 24 h.

⇒ **Interpretation:**

- In primary adrenal failure: No significant cortisol rise.
- In secondary adrenal failure: **gradually rises cortisol to a peak at 24 hours**
 - ❖ Prolonged stimulation of the adrenal glands by ACTH in the long Synacthen test → **gradually rises cortisol to a peak at 24 hours** → confirm the diagnosis of secondary adrenal failure.
 - ❖ in some cases of long-standing adrenal atrophy due to secondary adrenal insufficiency, the adrenal glands will not respond even after 24 hours and will require several daily doses of depot Synacthen before an adrenal response is seen.

- **CT or MRI of the brain to rule out a pituitary tumor or pituitary atrophy.**

Corticosteroids

Patients on long-term steroids should have their doses doubled during intercurrent illness

Mechanism of action

- Corticosteroids are hydrophobic small molecules and thus freely pass through cell membranes. They bind to inactive cytosolic glucocorticoid receptors, which then translocate to the nucleus to **act as nuclear transcription regulators**.

Summary of effects of systemic corticosteroids

- The relative glucocorticoid and mineralocorticoid activity of commonly used steroids is shown below:

Minimal glucocorticoid activity, very high mineralocorticoid activity	Glucocorticoid activity, high mineralocorticoid activity	Predominant glucocorticoid activity, low mineralocorticoid activity	Very high glucocorticoid activity, minimal mineralocorticoid activity
Fludrocortisone	Hydrocortisone	Prednisolone	Dexamethasone Betamethasone

Side-effects

- Glucocorticoid side-effects**

 - ⇒ **endocrine:**

 - impaired glucose regulation,
 - increased appetite/weight gain,
 - hirsutism,
 - hyperlipidaemia
 - Cushing's syndrome: moon face, buffalo hump, striae

 - ⇒ **musculoskeletal:**

 - osteoporosis,
 - proximal myopathy,
 - avascular necrosis of the femoral head

 - ⇒ **immunosuppression:**

 - increased susceptibility to severe infection,
 - reactivation of tuberculosis

 - ⇒ **psychiatric:** insomnia, mania, depression, **psychosis**

 - ⇒ **gastrointestinal:** peptic ulceration, acute pancreatitis

 - ⇒ **ophthalmic:** glaucoma, cataracts

 - ⇒ suppression of growth in children

 - ⇒ intracranial hypertension

- Mineralocorticoid side-effects**

 - ⇒ fluid retention

 - ⇒ hypertension

The pathogenesis of corticosteroid induced osteoporosis is multifactorial:

1. Corticosteroids **reduce osteoblastic activity**, and the resulting osteoblast/osteoclast imbalance causes loss of bone.

2. **Corticosteroids reduce intestinal calcium absorption** and lower circulating sex steroid levels.

Selected points on the use of corticosteroids:

- patients on long-term steroids should have their doses doubled during intercurrent illness
 - ⇒ For milder concurrent illnesses oral prednisolone is usually doubled for a few days.
 - ⇒ **For severe illness convert prednisolone temporarily to IV glucocorticoids,** conventionally 50-100 mg of hydrocortisone six hourly.
 - ⇒ **Mineralocorticoid dose is always left unchanged.**
- the BNF suggests gradual withdrawal of systemic corticosteroids if patients have: received more than 40mg prednisolone daily for more than one week, received more than 3 weeks treatment or recently received repeated courses
- **Low dose i.v hydrocortisone → improve outcome in sepsis**
 - ⇒ More recent randomised controlled trials have suggested that there is a benefit in sepsis when lower physiological doses of steroids are given.
- **Lactose-containing methylprednisolone preparations should not be used in patients with cows' milk allergy**
- Corticosteroids are recognised to **inhibit osteoblast activity and increase osteoblast apoptosis.** This is thought to be a more important component in bone loss with respect to steroid induced osteoporosis versus any effect on osteoclasts.
- Whilst corticosteroids do increase osteoclast activity, it is thought to be their effect on osteoblast activity which has a greater impact on bone mineral density.

Steroid induced hypogonadism

- Body builders may be involved in the illicit use of anabolic and androgenic steroids. These results are consistent with ongoing use of androgens.
- The hypogonadism, if persistent, may be treated with human chorionic gonadotropin.

Relative potencies of the glucocorticoids

- It is important to know the relative potencies of the glucocorticoids.
- **1 mg prednisolone is equivalent to 4 mg of hydrocortisone**
- Dexamethasone for instance is roughly 30 times more potent than hydrocortisone.

Steroid doses equivalence

- 1mg prednisolone = 4mg hydrocortisone
- 1mg dexamethasone = 7mg prednisolone
- Dexamethasone is roughly 30 times more potent than hydrocortisone.

Anabolic steroids

- Anabolic steroids can be taken orally (eg stanozolol) or may have to be injected because of their high first-pass metabolism (eg testosterone enantate)
- Among their many unwanted effects, they increase the risk of cardiovascular disease:
 - blood pressure is elevated
 - blood lipid profiles change, with increased LDL-cholesterol and decreased HDL-cholesterol
 - haematocrit is increased, leading to a prothrombotic tendency, although there is a protective **decrease in plasma fibrinogen concentrations with prolonged use**

Abuse of androgenic steroids

- The abuse of androgenic steroids amongst people who practise certain sports is quite common.
- **side effects**
 - ⇒ **Paranoid delusions**
 - ⇒ **aggressive behaviour.**
 - ⇒ Other side effects of these illicit drugs include:

- ⇒ Acne
- ⇒ Gynaecomastia (also increase in breast cancer risk)
- ⇒ Hypertension
- ⇒ Hypercholesterolaemia, and
- ⇒ Hepatic tumours.

Cushing's syndrome (Hypercortisolism)

Cushing's syndrome - hypokalaemic metabolic alkalosis

Small cell lung cancer accounts 50-75% of cases of ectopic ACTH

The overnight dexamethasone suppression test is the best test to diagnosis Cushing's syndrome

Pathological definition

- Cushing's syndrome → hypercortisolism from any cause.
- Cushing's disease → hypercortisolism caused by ACTH-secreting pituitary adenoma → the most common cause of Cushing's syndrome (75% of cases).

Epidemiology

- Commoner in ♀ (♀:♂, 3–15:1).
- Age: most commonly, 20–40 years

Causes

- **Exogenous (iatrogenic) Cushing syndrome**
 - ⇒ Prolonged glucocorticoid therapy → hypercortisolism → decreased ACTH → **bilateral adrenal atrophy**
 - ⇒ **Most common cause of hypercortisolism**
 - ⇒ Dexamethasone poses a higher risk for development of iatrogenic Cushing disease. Shorter-acting agents, such as prednisone or hydrocortisone, are recommended alternatives.
- **Endogenous Cushing syndrome**
 - ⇒ **Primary hypercortisolism (ACTH-independent Cushing syndrome)** (5–10%)
 - Autonomous overproduction of cortisol by the adrenal gland → ACTH suppression → atrophy of the contralateral adrenal gland
 - Adrenal adenomas
 - Adrenal carcinoma: **abnormal liver function tests (LFTs)** suggest metastases.
 - Adrenal hyperplasia
 - ⇒ **Secondary hypercortisolism (ACTH-dependent Cushing syndrome)**
 - **Pituitary ACTH production (Cushing disease)** (~75%): Pituitary adenomas → ACTH secretion → bilateral adrenal gland hyperplasia → **Undetectable serum ACTH level**
 - **Ectopic ACTH production** (~15%): Paraneoplastic syndrome (e.g. small cell lung cancer) → ↑ ACTH secretion → bilateral adrenal gland hyperplasia

- ☞ characteristically associated with very low potassium levels
- ☞ weight loss suggests there is an underlying malignancy → ectopic ACTH

Pseudo-Cushing's (Alcohol-induced Cushing's syndrome)

- **Obese alcoholic consumer** → ↑CRH secretion or impaired hepatic metabolism of cortisol → **cushingoid appearance** → Induce false positive dexamethasone suppression test or 24 hr urinary free cortisol
- **Investigations**
 - ⇒ **Midnight serum cortisol:** The most appropriate next step in the investigation of alcoholic patient after confirming hypercortisolism
 - The hallmark of true Cushing's syndrome is lack of diurnal variation in serum cortisol. However, in pseudo-Cushing's diurnal variation is normally maintained.
 - ⇒ **Insulin stress test** (insulin tolerance test)
 - used to differentiate between true Cushing's and pseudo-Cushing's
 - in pseudo-Cushing's the insulin tolerance test will demonstrate hypoglycaemia with a rise in ACTH and cortisol.
 - In Cushing's syndrome, this hypoglycaemia induced response is lost.
 - contraindicated in epilepsy, ischaemic heart disease, or hypoadrenalinism.
 - ⇒ **Raised MCV may point to alcoholism**
- **Management:** promote weight loss, and strict control of alcohol intake. Usually mild and disappears rapidly during abstinence from alcohol.

Features

- **Skin**
 - ⇒ Thin, easily **bruising** with ecchymoses
 - **Cortisol breaks down proteins in bone and skin , so the free amino acids can be used to make sugar.** This leads to bruising, striae, muscle wasting, and osteoporosis.
 - ⇒ Stretch marks (classically purple abdominal striae)
 - ⇒ Hirsutism, Acne: due to increased adrenal androgen levels
 - ⇒ Delayed wound healing
 - ⇒ Flushing of the face
 - ⇒ If secondary hypercortisolism: often hyperpigmentation (darkening of the skin due to an overproduction of melanin), especially in areas that are not normally exposed to the sun (e.g., palm creases, oral cavity)
 - Caused by excessive ACTH production because melanocyte-stimulating hormone (MSH) is cleaved from the same precursor as ACTH called proopiomelanocortin (POMC)
 - Not a feature of primary hypercortisolism
- **Neuropsychological:** lethargy, depression, sleep disturbance, psychosis
- **Musculoskeletal**
 - ⇒ Osteopenia, osteoporosis → pathological fractures, **avascular necrosis of the femoral head , vertebral collapse**
 - ⇒ Muscle atrophy/weakness (**proximal myopathy**)

- Endocrine and metabolic

- ⇒ Insulin resistance → hyperglycemia (see "Diabetes mellitus") → mild polyuria in the case of severe hyperglycemia
- ⇒ Dyslipidemia
- ⇒ **Fat redistribution:** "moon face," buffalo hump, truncal obesity, thin arms and legs
 - ⇒ ♂: Decreased libido
 - ⇒ ♀: Decreased libido, virilization, and/or irregular menstrual cycles (e.g., amenorrhea)

- Other features

- ⇒ Secondary hypertension (~ 90% of cases): due to fluid and sodium retention
- ⇒ Increased susceptibility to infections (due to immunosuppression)
- ⇒ Peptic ulcer disease
- ⇒ Cataracts
 - Most commonly → **Posterior subcapsular cataract**
 - The predominant feature of a posterior subcapsular cataract is glare when looking into bright lights, either from the sun or car headlights.
- ⇒ **Menstrual irregularity** is found in **84% of female** patients with Cushing syndrome

- General laboratory findings

- ⇒ Hyperglycemia (Diabetes mellitus may occur in 30%): Cortisol → ↑gluconeogenesis (from protein break down → free amino acids) → ↑glucose levels
- ⇒ Hyperlipidemia
- ⇒ Hypokalaemic
- ⇒ Metabolic alkalosis: caused by increased urinary loss of H⁺ (acid)
- ⇒ Leukocytosis
- ⇒ Low oestradiol

Diagnosis: confirm Cushing's syndrome (hypercortisolism) and then localise the lesion.

- Tests to confirm Cushing's syndrome (hypercortisolism) : the two commonly used are:

1. **Overnight low dose (1 mg) dexamethasone suppression test (ODST)**
 - **Sensitivity and specificity are 98% (most sensitive)**
 - **Low sensitivity and specificity in obese subjects (75-80%) therefor (UFC) will be best than (ODST) in obese**
 - If cortisol is suppressed → **Cushing's disease** is the likely cause.
 - If cortisol is not suppressed → either **primary adrenal Cushing's syndrome** (low/undetectable ACTH) or **ectopic ACTH** is the cause (high ACTH).
 - **Causes of false-positive ODST** (meaning that a diagnosis of Cushing is suggested incorrectly)
 - ☞ **cytochrome p450 inducers** (Dexamethasone is metabolised by the cytochrome p450 system, specifically by the CYP3A4 isoenzyme).
 - ☞ **↑oestrogen exposure** (eg, pregnancy, oral contraceptives)
 - ↑corticosteroid-binding globulin (CBG): need 6 weeks washout before the test
 - If ODST is not offered in a question, then 24 hour urinary free cortisol is the next best answer
2. **24 hr urinary free cortisol (UFC)**
 - ⇒ Can be useful for **outpatient screening**

- ⇒ Due to false -ve rate of 10% it should not be used alone. **should be followed by an overnight dexamethasone suppression test. If both of these tests** are normal, then Cushing syndrome could be ruled out.
- ⇒ Factors lead to false +ves: Fenofibrate, carbamazepine, and digoxin.

- **Tests to localise the lesion (source of the hypercortisolism):**

- 1) **The first step is to measure ACTH level:**
 - **ACTH level low:** This means the origin is in the adrenal gland → Scan the gland with a CT or MRI.
 - **ACTH level high:** This means the origin is either in the pituitary gland or from the ectopic production of ACTH.
- 2) **The next step is a high-dose (8 mg) dexamethasone suppression test (to differentiate between Cushing disease and ectopic ACTH production)**
 - If high-dose dexamethasone suppresses the ACTH → adequate suppression of cortisol levels to less than 50% of baseline: the origin is the **pituitary**. Scan the pituitary.
 - If high-dose dexamethasone **does not suppress the ACTH** (No cortisol suppression): the origin is an **ectopic** production of ACTH or a cancer that is making ACTH. Scan the chest for lung cancer or carcinoid.
 - ☞ **Serum cortisol levels would remain unchanged with both low-level and high-level dexamethasone testing due to the lack of glucocorticoid receptors** to facilitate negative feedback **on the ectopic cells producing the ACTH**. Anterior pituitary corticotrophs do have these receptors and, therefore, will be suppressed by any dose of dexamethasone.
 - The use of high-dose dexamethasone suppression testing is an area of debate, owing to its variable sensitivity and specificity.
- 3) **CRH stimulation test**
 - ACTH and cortisol levels increase further: Cushing disease
 - No increase in ACTH or cortisol levels: ectopic ACTH production
- 4) **Inferior Petrosal sinus sampling (IPSS)**
 - **IPSS is the only test with sufficient diagnostic accuracy to differentiate Cushing's disease from ectopic ACTH production** (the test of choice)
 - Patient with high ACTH without definitive lesions on MRI should undergo IPSS: Up to 40% of patients with Cushing's disease will not have visible lesions on pituitary/sellar MRI. (The overall sensitivity of MRI to diagnose Cushing disease is only 60% to 70%).
 - It samples venous blood draining from the pituitary gland, using a femoral approach. A raised ACTH from here compared to the periphery suggests a pituitary cause.
 - Patients with an IPSS central/peripheral gradient of ACTH $>2:1$ or $3:1$ after corticotrophin-releasing hormone (CRH) stimulation → Cushing's disease
 - Patients without high central/peripheral gradient of ACTH → ectopic ACTH → do CT of the chest, abdomen, and pelvis to look for a tumour secreting ACTH.
 - ☞ The most common tumours that secrete ACTH are bronchial or thymic carcinoids.

Dexamethasone suppression tests

- The low-dose (1 mg) dexamethasone suppression test: used to **confirm Cushing's syndrome (hypercortisolism)**
- The high-dose (8 mg) dexamethasone suppression test: used to **differentiate between Cushing disease and ectopic ACTH production.**

If a **24-hour urine free cortisol is elevated (one evidence of hypercortisolism)**, and there is an **inadequate suppression on 1 mg overnight dexamethasone test (confirmatory test for hypercortisolism)** in a patient suspected of Cushing syndrome, the next step would be to measure **ACTH (to localise the lesion)**

The following table summarizes the characteristics of the 3 sources of Cushing disease.

	Pituitary Tumor	Ectopic ACTH Production	Adrenal Adenoma
ACTH	High	High	Low
High-dose dexamethasone	Suppression	No suppression	No suppression
Specific test	MRI, Petrosal vein sampling	Scan chest and abdomen	Scan adrenals
Treatment		Removal	

Which techniques is the best in differentiating between ectopic Cushing's syndrome and pituitary dependent Cushing's disease?

- ⇒ **Inferior petrosal sinus sampling**
- ⇒ The high-dose dexamethasone suppression test can differentiate between the two forms of Cushing's syndrome, but is not as accurate as inferior petrosal sinus sampling.

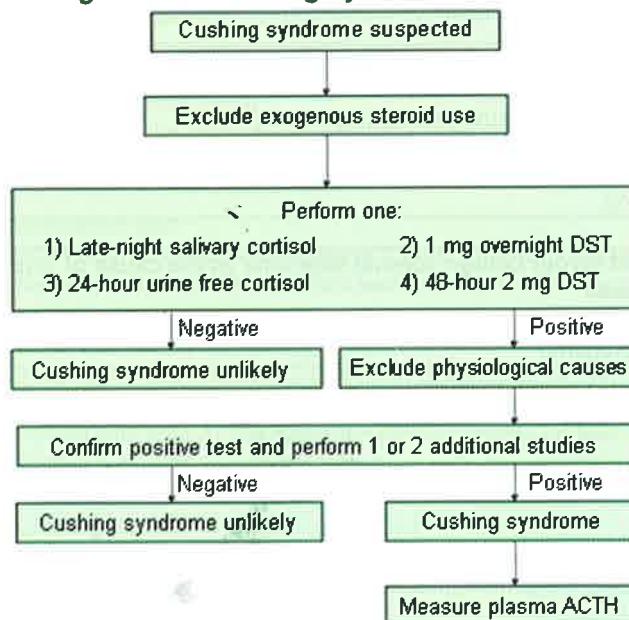
Which feature would favour benign adrenal adenoma as the cause of Cushing's syndrome over the other causes?

- ⇒ **Absence of hirsutism and virilisation** (adrenal adenoma produces cortisol but not the androgens)

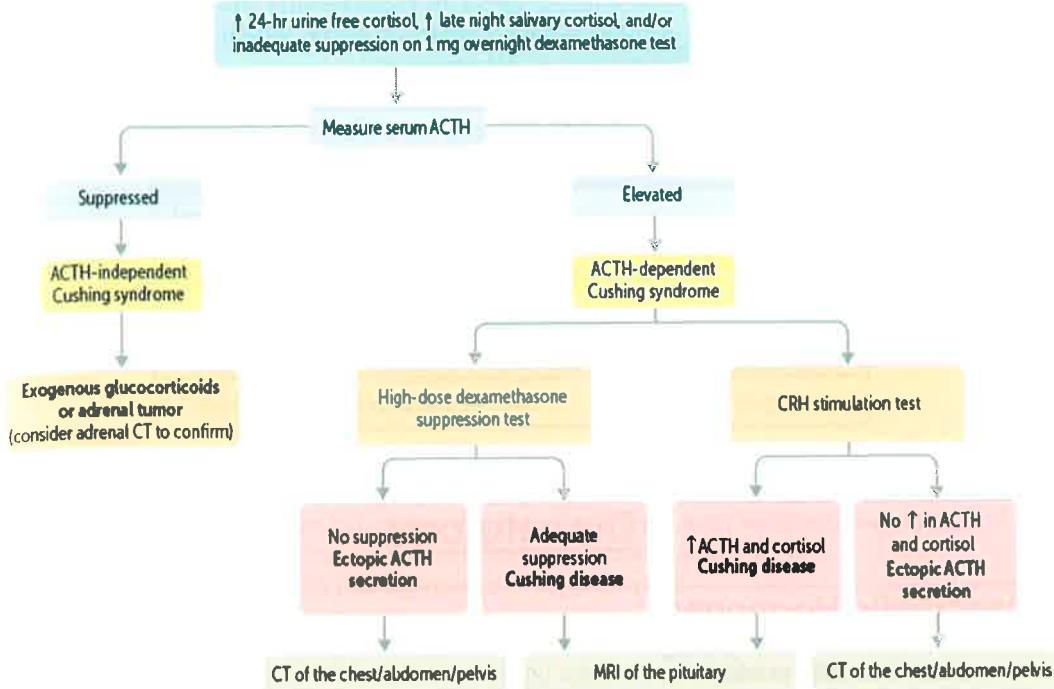
Diagnostic steps in suspected Cushing's syndrome

- **Step 1:** Exclude exogenous corticosteroid use
- **Step 2:** Screen for hypercortisolism with 1 of the 4 high-sensitivity tests
 - 1) late-night salivary cortisol;
 - 2) 1 mg overnight low-dose dexamethasone suppression testing,
 - 3) 24-hour urinary free cortisol; or
 - 4) 48-hour 2 mg dexamethasone suppression testing.
- **Step 3:** Exclude physiological causes of hypercortisolism (from history)
 - ⇒ physical stress, malnutrition, alcoholism, depression, pregnancy, class III obesity (BMI 40 or above) or metabolic syndrome.
- **Step 4:** If an initial screening test is positive, and physiological causes of hypercortisolism have been excluded: confirm hypercortisolism with at least 1 additional test of the 4 high-sensitivity tests.
- **Step 5:** Once endogenous hypercortisolism is confirmed, **plasma ACTH** should be measured.
 - ⇒ If ACTH is suppressed, diagnostic testing should focus on the adrenal glands. → adrenal CT → adenoma.
 - ⇒ If ACTH is not suppressed, pituitary or ectopic disease should be sought.

Algorithm for the diagnosis of Cushing syndrome



In the diagnosis of hypercortisolism, **hormone analysis always precedes imaging** because microadenomas of the pituitary do not always appear upon imaging. Furthermore, imaging can reveal inactive adrenal tumors (incidentalomas) and pituitary tumors in many healthy individuals.



Treatment

- **Fit for surgery**
 - ⇒ Pituitary adenoma → Trans-sphenoidal hypophysectomy/adenomectomy is the initial treatment of choice.
 - ⇒ Adrenocortical tumor: laparoscopic or open adrenalectomy
 - ⇒ Laparoscopic adrenalectomy would be advised where pituitary surgery has failed.
 - ⇒ The recurrence rate for Cushing's disease after surgery is 20-30% and depends on the size of the tumour with macroadenomas having a higher rate of relapse.
 - ⇒ ACTH-secreting ectopic tumor: resection of the ectopic foci (e.g., bronchial carcinoid)
- **Unfit for surgery**
 - ⇒ **Ketoconazole may be an effective treatment for patients unfit for surgery**
 - ⇒ **Mitotane** is an adrenolytic drug licensed for symptomatic treatment of advanced or inoperable adrenocortical carcinoma → **improve the prognosis**

Which drug is most appropriate to improve metabolic parameters prior to surgery in pituitary-dependent Cushing's?

⇒ **Metyrapone** → inhibits 11-beta hydroxylase → inhibits cortisol production.

What is the optimum time for the administration of hydrocortisone to a patient undergoing bilateral adrenalectomy for Cushing's disease?

⇒ **Immediately following the removal of both adrenal glands.**

Perioperative management of a cortisol producing adenoma includes:

- **Peri and postoperative hydrocortisone with further assessment of postoperative cortisol secretion**

May 2008 exam: A 62-year-old man is investigated for hypertension and proximal myopathy. On examination he is noted to have abdominal striae. Which one of the following is most associated with ectopic ACTH secretion?

⇒ Small cell lung cancer

Disorder	Investigation of choice
Cushing	Overnight Dexamethasone Test
Cushing- vs. Pseudo-cushing	Insulin Stress Test
Addison	Short Synacthen Test
Pheochromocytoma	24H Urinary metanephrenes
Acromegaly	Oral Glucose Tolerance Test

Diabetology

Pancreatic Hormones

- Islet A cells produce **glucagon**
- **Islet beta cells produce:**
 1. insulin
 2. C peptide
 3. pro-insulin
 4. amylin
 5. GABA
- Islet D cells produce **somatostatin**
- F cells produce **pancreatic polypeptide**

Glucose transporters

Glucose entrance to the cells

- To intestinal epithelial cells and proximal renal tubular cells → via **Sodium/Glucose cotransporter (SGLT)**
- To all other cells of the body → **Glucose Transporters (GLUTs)**.

Sodium/glucose cotransporter (SGLT)

- Glucose uptake into the enterocyte from the lumen of the GI tract occurs primarily via the sodium-dependent **SGLT-1** secondary active transport mechanism.
 - ⇒ SGLT-1 is a transporter found predominantly in the gut, and is responsible for glucose absorption.
 - ⇒ The Na⁺-glucose cotransporter also transports galactose. Thus, when the cotransporter is congenitally defective, the resulting glucose and galactose malabsorption causes severe diarrhea that can be fatal if glucose and galactose are not removed from the diet.
- Function
 - ⇒ **transport glucose actively across lumen against concentration gradient**
 - energy provided by transport of sodium down its concentration gradient

- location
 - ⇒ **small intestine (SGLT1)** → 2:1 Na⁺:Glu
 - ⇒ **proximal tubule of nephron (SGLT2)** → 1:1 Na⁺:Glu
- Glucose exit from the enterocyte into the extracellular fluid occurs by facilitated diffusion and is mediated by the membrane transporter, **Glut-2**.

Glucose Transporters (GLUTs).

GLUT-1

- function
 - ⇒ basal glucose uptake (GLUT1 and GLUT3 continually transport glucose into cells at an essentially constant rate.)
 - high affinity
 - ❖ transporters saturated at normal blood glucose levels
 - ❖ ensures glucose entry to cells
- location
 - ⇒ wide distribution in tissues in the body (brain, erythrocytes, endothelial cells, cornea etc.)
 - ⇒ especially expressed in cells with barrier functions, such as Blood- Brain barrier, blood-retinal barrier, blood placental barrier, blood testes barrier
 - ⇒ **most importantly it is expressed in erythrocytes.**

GLUT-2

- GLuT 2 is a glucose transporter expressed in **pancreatic beta cells**.
- It is a fundamental part of the glucose sensing apparatus in the pancreatic beta cells and helps trigger insulin release in response to increasing glucose concentrations in the extracellular fluid.
- GLuT 2 is also expressed in hepatocytes and may act as a glucose sensor in the portal vein system.
- It may have a role in regulating glucagon secretion and feeding behaviour.
- function
 - ⇒ **low affinity glucose uptake** (high-capacity but a low affinity transporter)
 - in the fasting state glucose does not enter cells
 - mediates glucose surplus storage in liver when blood glucose levels rise
 - **facilitates insulin release in β-cells**
- location
 - ⇒ hepatocytes
 - ⇒ **pancreatic β-cells**
 - ⇒ kidney
 - ⇒ small intestines

In healthy individuals, which glucose transporter is required for triggering insulin secretion in response to elevated blood glucose concentration?

⇒ **GluT 2**

GLUT-3

- function
 - ⇒ high affinity glucose uptake
 - glucose preferentially accessed by neurons in low-glucose states
- location
 - ⇒ **brain**
 - ⇒ **neurons**

GLUT-4

- GLUT-4 is the only glucose transporter that is responsive to circulating insulin levels.
 - ⇒ ↑ plasma glucose concentration → ↑ circulating insulin → ↑ expression of GLUT-4 → ↑ glucose transport into the cell.
 - ⇒ The other types of glucose receptors (GLUT-1,2,3,&5) are not responsive to circulating insulin levels
 - ⇒ exogenous insulin in the treatment of diabetes mellitus results in increased glucose uptake via the GLUT-4 transporter.
 - ⇒ This high-affinity glucose transporter plays a crucial role in avoiding postprandial hyperglycemia, since insulin secreted by the pancreatic beta cells promotes glucose uptake into myocytes.
- function
 - ⇒ insulin-controlled uptake of glucose
 - ⇒ basal level of glucose intake without insulin
 - presence of insulin ↑ translocation of transporters to the cell membrane
 - ❖ ↑↑ glucose uptake
 - ❖ also stimulated by exercise
- location
 - ⇒ adipocytes
 - ⇒ myocytes
 - ⇒ cardiomyocytes

Which glucose transporter is responsible for assisting glucose across the plasma membrane in myocytes?

⇒ GLUT 4

Glut-5

- located on the apical portion of the enterocyte
- function: entry of fructose into the cell.

- GLUT-1 = BBB (Blood- Brain barrier)
- GLUT-3 = "Brain"

Glycaemic index (GI)**Definition**

- The glycaemic index (GI) describes the capacity of a food to raise blood glucose compared with glucose in normal glucose-tolerant individuals.

Classification

- Carbohydrates can be scored from 0 to 100 where glucose has a GI of 100.
- High GI index foods have a value of 70 or above, medium 56-69 and low <55.
- Apples, peaches oranges and even chocolate are considered low GI (less than 55).
- through different preparation, the GI can alter – mashed potatoes (70) and baked potatoes (85) have a high GI (above 70) whilst boiled potatoes have a moderate GI of 58.
- Foods only appear if they contain carbohydrate hence meats, eggs and fish do not appear in the GI index.
- Generally, the lower the GI index the 'better' the carbohydrate.

Classification	Examples
High GI	White rice (87), baked potato (85), white bread (70)
Medium GI	Couscous (65), boiled new potato (62), digestive biscuit (59), brown rice (58)
Low GI	Fruit and vegetables, peanuts

The risk of foods with a high GI

- may be associated with an increased risk of obesity
- the post-prandial hyperglycaemia associated with such foods may also increase the risk of type 2 diabetes mellitus.

Metabolic syndrome

Features of the metabolic syndrome are:

- Diabetes or pre-diabetes.
- Hypertension
- Central adiposity
- High triglycerides or low HDL cholesterol**

Definition

- the co-occurrence of metabolic risk factors for both type 2 diabetes and cardiovascular disease (CVD) (abdominal obesity, hyperglycemia, dyslipidemia, and hypertension).

Pathophysiology

- the key pathophysiological factor is insulin resistance.

Diagnostic criteria

- WHO** criteria (1999): Presence of **insulin resistance** (type 2 diabetes mellitus , impaired glucose tolerance, or impaired fasting glucose), **Plus** two of the following:
 - blood pressure: > 140/90 mmHg
 - dyslipidaemia: **triglycerides**: > 1.695 mmol/L and/or high-density lipoprotein cholesterol (HDL-C) < 0.9 mmol/L (male), < 1.0 mmol/L (female)
 - central obesity: waist: hip ratio > 0.90 (male), > 0.85 (female), and/or body mass index > 30 kg/m²
 - microalbuminuria: urinary albumin excretion ratio > 20 mg/min or albumin: creatinine ratio > 30 mg/g
- International Diabetes Federation** criteria (2005): presence of **central obesity** (defined as waist circumference > 94cm for Europid men and > 80cm for Europid women, but can be assumed if BMI >30 kg/m²) **Plus** two of the following:
 - Triglycerides**: > 1.7 mmol/L, or specific treatment for this lipid abnormality
 - HDL cholesterol: < 1.03 mmol/L in males and < 1.29 mmol/L in females, or specific treatment for this lipid abnormality.
 - BP: > 130/85 mm Hg, or active treatment of hypertension
 - Fasting glucose > 5.6 mmol/L**, or previously diagnosed type 2 DM.

Management

- Aggressive lifestyle modification focused on weight reduction and increased physical activity
- Long-term **exercise upregulates expression of GLUT4**, which may reduce hyperglycemia in patients with type 2 DM or metabolic syndrome.
- Orlistat** (an inhibitor of gastrointestinal lipases) **with diet**, **reduces the risk of diabetes in an obese patients** by 38% more than diet alone.

Alström syndrome (AS)

- rare autosomal recessive disease
- caused by mutations in the ALMS1 gene.
- characterized by multiorgan dysfunction.
- Key features are:
- **childhood obesity, hyperinsulinemia, early-onset type 2 diabetes, and hypertriglyceridemia.** Thus, AS shares several features with the common metabolic syndrome, namely obesity,
- blindness due to **congenital retinal dystrophy**,
- sensorineural hearing loss.
- dilated cardiomyopathy in over 60% of cases,
- developmental delays in 50 % of cases.

Pre-diabetes or impaired glucose regulation (IGR)**Definition:**

- impaired glucose levels which are above the normal range but not high enough for a diagnosis of diabetes mellitus. Includes impaired fasting glucose (IFG) and impaired glucose tolerance (IGT).
- Diabetes UK currently recommend using the term prediabetes when talking to patients and impaired glucose regulation (IGR) when talking to other healthcare professionals

Incidence

- Diabetes UK estimate that around **1 in 7** adults in the UK have prediabetes.

Impaired fasting glucose (IFG)

- Definition → fasting glucose greater than or equal to 6.1 but less than 7.0 mmol/l
 - ⇒ Mechanism → **due to hepatic insulin resistance**
 - ⇒ people with IFG should then be offered an oral glucose tolerance test (OGTT) to rule out a diagnosis of diabetes.

Impaired glucose tolerance (IGT)

- Definition → fasting plasma glucose less than 7.0 mmol/l and OGTT 2-hour value greater than or equal to 7.8 mmol/l but less than 11.1 mmol/l
- Mechanism → due to **muscle insulin resistance**
- Patients with IGT are more likely to develop T2DM and cardiovascular disease than patients with IFG

Identification of patients with prediabetes: Who should be assessed for the risk of type 2 diabetes?

- all adults aged 40 and over,
- people of South Asian and Chinese descent aged 25-39,
- adults with conditions that increase the risk of type 2 diabetes:
 - ⇒ cardiovascular disease, stroke, hypertension,
 - ⇒ obesity,
 - ⇒ polycystic ovary syndrome,
 - ⇒ history of gestational diabetes
 - ⇒ mental health problems.

Diagnosis

	normal	Prediabetes	Diabetes mellitus
Fasting glucose	≤ 6 mmol/l	$\geq 6.1 - 6.9$ mmol/l impaired fasting glucose (IFG)	≥ 7 mmol/l
2h glucose during an OGTT	< 7.8 mmol/l	$7.8 - 11$ mmol/l Impaired glucose tolerance (IGT)	≥ 11.1 mmol/l
HA1c	< 42 mmol/mol $< 6\%$	$42 - 47$ mmol/mol ($6.0 - 6.4\%$)	$\geq 6.5\%$

Complication

- progression to type 2 diabetes mellitus (T2DM)
- **The risk of developing type 2 diabetes in patient with (IGT) → 60% over 6 years**
- ↑ risk of macrovascular disease (e.g. coronary artery disease). No risk of microvascular complications of diabetes such as retinopathy and nephropathy.

Management

The best way to reduce the incidence of type 2 diabetes in individuals with IGT is → Intensive lifestyle change

- Lifestyle modification: weight loss, increased exercise, change in diet
 - ⇒ intensive diet and lifestyle change (that results in loss of approximately 5% of initial body weight) can reduce progression from impaired fasting glucose (or impaired glucose tolerance) to frank type 2 diabetes by approximately 50%.
- NICE recommend metformin for adults at high risk 'whose blood glucose measure (fasting plasma glucose or HbA1c) shows they are still progressing towards type 2 diabetes, despite their participation in an intensive lifestyle-change programme'

Which drug classes is most well known as a cause of impaired glucose tolerance?

⇒ **Atypical antipsychotics**

Both typical antipsychotics and antihypertensives (thiazides and beta blockers), have been shown in meta-analyses to be associated with impaired glucose tolerance and increased risk of type 2 diabetes.

The risk is relatively larger for risperidone than thiazides & β.blocker

MRCPUK- part- 1-September 2009 exam: The fasting glucose of asymptomatic patient comes back as 6.5 mmol/l. The test is repeated and reported as 6.7 mmol/l. How should these results be interpreted? **Impaired fasting glycaemia**

Diabetes mellitus: Type 1 overview

Definition

- Type 1 diabetes mellitus is a metabolic disorder characterised by hyperglycaemia due to absolute insulin deficiency.

Epidemiology

- 5% to 10% of all patients with diabetes.
- more common in Europeans and less common in Asians.

Pathophysiology

- Genetic susceptibility and environmental triggers** (often associated with previous viral infection) → **autoimmune response** (CD4 +T-cell mediated) with production of **autoantibodies**, e.g., anti-glutamic acid decarboxylase antibody (anti-GAD), anti-islet cell cytoplasmic antibody (anti-ICA) → progressive **destruction of β cells** in the pancreatic islets → **absolute insulin deficiency** → decreased glucose uptake in the tissues.
- Type 1 diabetes becomes clinically evident upon destruction of approximately 70-80 % of beta cell mass.

Risk factors

- Genetic risks**
 - ⇒ **HLA association** (HLA DR4 > HLA DR3)
 - ⇒ **The familial risk of Type 1 diabetes:**
 - Only 10% of patients have a positive family history
 - If both parents have type 1 DM → ≈ 40% (in offspring)
 - If the father has type 1 DM → 3–6%
 - If the mother has type 1 DM → 2–3%
 - If one identical twin has type 1 DM, the risk in the unaffected twin → 30–50%.
 - If a sibling (brother or sister) has type 1 diabetes → 5–6%
- Viral infections**
 - ⇒ Only congenital rubella infection has been definitively linked to an increased risk for type 1 diabetes.
 - ⇒ Studies attempting to link other viruses to type 1 diabetes, including enterovirus and rotavirus, have had mixed results.
 - ⇒ Enteroviruses may play a role in both protection from and susceptibility to type 1 diabetes.
- Presence of **autoantibodies** → 50% risk of DM over five years.
- Loss of first phase insulin response** (postprandial insulin secretion in response to a meal, begins within 2 minutes of nutrient ingestion and continues for 10 to 15 minutes) → indicator of significant impending beta cell destruction → 100% risk of DM over two years.
- Association with other autoimmune conditions**
 - ⇒ Hashimoto thyroiditis
 - ⇒ Type A gastritis
 - ⇒ Celiac disease
 - ⇒ Primary adrenal insufficiency

Which feature is most closely associated with the imminent development of type 1 diabetes? → Loss of first phase insulin response

Features

- Age of onset below 50 years
- Diabetic ketoacidosis (DKA) is the first manifestation in one-third of cases
- **BMI below 25 kg/m²**
- Rapid weight loss (**the cardinal feature** of absolute insulin deficiency.)
- Classic symptoms of hyperglycemia (Polyuria, Polydipsia, Polyphagia)
- Increased susceptibility to infections

Weight loss is an indicator of type 1DM even if the patient is obese → insulin is the best treatment (SCE. Questions sample. Mrcpuk.org)

Diagnosis of DM: any one of the following

- Fasting plasma glucose ≥ 126 mg/dL (7 mmol/L) on at least two occasions
- Symptoms of hyperglycemia and a plasma glucose ≥ 200 mg/dL (11.1 mmol/L)
- Plasma glucose ≥ 200 mg/dL (11.1 mmol/L) measured two hours after a standard glucose load in an oral glucose tolerance test
- Glycated hemoglobin (A1C) $\geq 6.5\%$.

Investigations for type 1

- **C-peptide**
 - ⇒ ↓ C-peptide levels indicate an absolute insulin deficiency → type 1 diabetes
 - ⇒ ↑ C-peptide levels may indicate insulin resistance and hyperinsulinemia → type 2 diabetes
- **Antibodies** detected in patients who later go on to develop type 1 DM:
 - ⇒ Glutamic Acid Decarboxylase (**GAD**) antibody
 - **found in 70-90% of type 1 diabetics.**
 - 10 fold increases the risk of developing IDDM.
 - 10% of adults who have been classified as having type 2 diabetes may have (ICA) or (GAD) antibodies, indicating autoimmune destruction of beta cells.
 - ⇒ Islet Cell Antibodies (ICA): **found in up to 60 - 80% of patients with type 1 diabetes**

Complications

- **Microvascular complications** include retinopathy, nephropathy, and neuropathy.
- **Macrovascular complications** include cerebrovascular, coronary artery, and peripheral vascular disease.

Diabetes mellitus: management of type 1

In newly diagnosed adults with type 1 diabetes, the first-line insulin regime should be a basal–bolus using twice-daily insulin detemir.

Diet

- Do not advise adults with type 1 diabetes to follow a low glycaemic index diet for blood glucose control.

Insulin

- **Insulin injection regimen:** offer multiple daily injection basal–bolus insulin regimens, rather than twice-daily mixed insulin regimens, as the insulin injection regimen of choice.
- **For basal insulin:**
 - ⇒ **twice-daily insulin detemir is the regime of choice.** Once-daily insulin glargine is an alternative.
 - ⇒ once-daily ultra-long-acting insulin such as degludec, if there is a concern about nocturnal hypoglycaemia or for people who need help from a carer.
- **For mealtime insulin:** offer rapid-acting insulin **analogues** injected before meals, rather than rapid-acting soluble human or animal insulins.
- **Insulin dose:** normal insulin requirements are around 0.5–0.6 units/kg/day, split equally between background (basal) and mealtime (bolus) requirements
- **Insulin dose adjustments**
 - ⇒ During periods of illness: the TREND UK guidance advises that:
 - If blood glucose is less than 13 mmol/L and no ketones are present then insulin should be taken as normal.
 - If blood glucose is more than 13 mmol/L and ketones are present then insulin adjustment is needed. add 10% of the daily insulin dose as rapid acting insulin every four hours, and then four hourly glucose and ketone monitoring to guide ongoing dosage/management.
 - ⇒ After alcohol or exercise → reduce evening basal insulin by 25–50%.

Metformin

- NICE recommend considering adding metformin if the $BMI \geq 25 \text{ kg/m}^2$

Referral indication for islet or pancreas transplantation

- type 1 diabetes with recurrent severe hypoglycaemia that has not responded to other treatments
- type 1 diabetes with suboptimal diabetes control who have had a renal transplant and are currently on immunosuppressive therapy.

Monitoring

- **Frequency of self-monitoring of blood glucose**
 - ⇒ recommend testing at least 4 times a day, including before each meal and before bed.
 - ⇒ more frequent monitoring is recommended if frequency of hypoglycaemic episodes increases; during periods of illness; before, during and after sport; when planning pregnancy, during pregnancy and while breastfeeding.
 - ⇒ during periods of illness, blood glucose and ketones should be checked at least every 4 hours.

Targets

Test	Targets
HbA1c	$\leq 48 \text{ mmol/mol (6.5\%)}$
fasting plasma glucose	5–7 mmol/litre on waking
	4–7 mmol/litre before meals
Post-prandial	5–9 mmol/litre (< 10)
during surgery or acute illness	5–8 mmol/litre
blood pressure	135/85 mmHg

Impaired fasting glucose and impaired glucose tolerance

- **Impaired fasting glucose (IFG)** is defined as fasting glucose ≥ 6.1 but $< 7.0 \text{ mmol/l}$
- **Impaired glucose tolerance (IGT)** is defined as fasting glucose $< 7.0 \text{ mmol/l}$ and OGTT 2-hour $\geq 7.8 \text{ mmol/l}$ but $< 11.1 \text{ mmol/l}$

Diabetes mellitus: Type 2 overview

Definition

- Type 2 diabetes mellitus is a progressive disorder defined by deficits in insulin secretion and increased insulin resistance

Epidemiology

- greater incidence among those of black and South Asian origin.
- Most are over 40yrs, but teenagers are now getting type 2 DM

Genetics

- Polygenic
- No HLA associations.
- Strong familial predisposition. Familial risks for developing diabetes
 - ⇒ **Concordance between identical twins is higher in type 2 diabetes mellitus than type 1**
 - ⇒ **if one identical twin has type 2 diabetes, the risk in the unaffected twin → 60 – 100 %.**
 - ⇒ **The incident diabetes risk in siblings and offspring of patients with type 2 diabetes is approximately 10%.**
 - ⇒

Pathophysiology

- **Peripheral insulin resistance**
 - ⇒ **Obesity** → ↓ **Adiponectin (secreted by adipocytes)** and involved in lipid catabolism) → **insulin resistance** (inversely correlated with the risk for diabetes).
 - ⇒ Central obesity → ↑ free fatty acids → impaired insulin-dependent glucose uptake into hepatocytes, myocytes, and adipocytes
 - ⇒ ↑ **Plasminogen activator inhibitor 1** (↑ in obesity & ↓ in weight loss → **insulin resistance** → **type 2 diabetes mellitus**.)

- **Beta cell dysfunction:** accumulation of pro-amylin (islet amyloid polypeptide) in the pancreas → decreased endogenous insulin production
 - ⇒ Amyloid deposition → ↓ islet cell number and function.
 - ⇒ The presence of amyloid polypeptide on pancreatic histology is highly suggestive of type 2 DM.
 - ⇒ Beta cell function is reduced by up to 70% at the point of type 2 diabetes diagnosis.
 - ⇒ The earliest manifestation of beta cell dysfunction occurs in the form of reduced and delayed postprandial early phase insulin secretion.
- **Alpha cell dysfunction** → ↑ plasma glucagon
- **Secondary diabetes** (e.g. Haemochromatosis)

Risk factors

- Age, ethnicity and positive family history
- Conditions associated with insulin resistance: e.g., severe obesity, dyslipidemia
- Polycystic ovary syndrome
- Physical inactivity
- Hypertension
- History of gestational diabetes

Features

- The majority of patients are asymptomatic.
- Elderly patients may present in a hyperosmolar hyperglycemic state.
- Symptoms of hyperglycemia (Polyuria, Polydipsia Polyphagia)
- Prone to recurrent infections
 - ⇒ DM → Impaired neutrophil chemotaxis and phagocytosis → immunosuppression → recurrent infections
- 30% of patients presenting with acute coronary syndrome will have undiagnosed type 2 DM
- Increased concentrations of C peptide are a marker of increased colorectal cancer risk

Diagnosis: WHO criteria

- Fasting plasma glucose ≥ 7.0 mmol/L (≥ 126 mg/dL), or
- Plasma glucose ≥ 11.1 mmol/L (≥ 200 mg/dL) 2 hours after 75 g oral glucose, or
- Glycosylated haemoglobin (HbA1c) ≥ 48 mmol/mol ($\geq 6.5\%$), or
- In a symptomatic patient, random plasma glucose of ≥ 11.1 mmol/L (≥ 200 mg/dL).
- Repeat confirmatory test is required in asymptomatic patients.

Diabetes diagnosis: fasting > 7.0 , random > 11.1 - if asymptomatic need two readings.

Beta cell mass

- Compared with subjects with normoglycaemia,
 - ⇒ beta cell mass is reduced by 50% in subjects with Impaired Fasting Glucose,
 - ⇒ by 70% in subjects with Type 2 diabetes, and
 - ⇒ over 90% in subjects with type 1 diabetes.

Diabetes UK suggests : 'People with IFG should then be offered an oral glucose tolerance test to rule out a diagnosis of diabetes. A result below 11.1 mmol/l but above 7.8 mmol/l indicates that the person doesn't have diabetes but does have IGT.'

Which lipid abnormalities are most likely to be detected in a patient with type 2 diabetes?
 → Small dense LDL molecules

Glycosylated haemoglobin (HbA1c)

Diabetes mellitus - HbA1c of 6.5% or greater is now diagnostic (WHO 2011)

Indications

- Diagnosis of diabetes mellitus and prediabetes state.
 - ⇒ Normal level → < 42 mmol/mol (< 6%)
 - ⇒ An HbA1c of 6.5% is recommended as the cut point for diagnosing diabetes.
 - ⇒ Prediabetes → 42 – 47 mmol/mol (6.0 – 6.4%)
 - ⇒ Diabetes mellitus → ≥ 6.5%
- Measure of long-term glycaemic control in diabetes mellitus.
 - ⇒ Reflects average blood glucose over the previous 2 - 3 months.

Follow up intervals

- NICE recommend '*HbA1c should be checked every 3-6 months until stable, then 6 monthly*'.

Methods of reporting :

- Percentage vs mmol/mol
 - ⇒ A new internationally standardised method for reporting HbA1c has been developed by the International Federation of Clinical Chemistry (IFCC). This will report HbA1c in mmol per mol of haemoglobin without glucose attached.

HbA1c (%)	IFCC-HbA1c (mmol/mol)
6	42
7	53
8	64
9	75

- Estimated average glucose

HbA1c (%)	Average plasma glucose (mmol/l)
5	5.5
6	7.5
7	9.5
8	11.5
9	13.5
10	15.5
11	17.5
12	19.5

- Equations**

- ⇒ New mmol/mol = [Old % - 2.15] x 10.929
- ⇒ Old % = [New mmol/mol divided by 10.929] + 2.15
- ⇒ Average plasma glucose = (2 * HbA1c) - 4.5

HbA1c targets

- For diabetic patient on lifestyle + metformin → 48 mmol/mol (6.5%)
- For diabetic patient on drug which may cause hypoglycaemia (e.g. lifestyle + sulfonylurea) → 53 mmol/mol (7.0%)

Unexpected or discordant HA1C values

- When there is a disparity between the A1C values and blood glucose values, we rely on the glucose values.
- Use frequent glucose monitoring. Fructosamine or glycated albumin may be useful alternatives.

The level of HbA1c therefore is dependent on:

- red blood cell lifespan
- average blood glucose concentration

Falsey high A1C values

- Low red cell turnover
 - ⇒ vitamin B12
 - ⇒ folate deficiency anemia.
- Splenectomy : spleen removes old RBCs. Not having a spleen increases RBC life span.

Falsey low A1C values

- Rapid red cell turnover
 - ⇒ Chronic hemolysis (eg, thalassemia, glucose-6-phosphate dehydrogenase deficiency);
 - ⇒ patients treated for iron, vitamin B12, or folate deficiency; and patients treated with erythropoietin.
- Blood transfusion (factitiously low A1C level)
- Advanced chronic kidney disease, haemodialysis
- Alcohol consumption**
- Sudden weight loss**

If A1C is higher than expected based on the mean glucose results

- Do fingerstick blood glucose levels between meals or short-term use of continuous glucose monitoring (CGM) to evaluate glucose patterns. One explanation is that the postprandial glucose is higher than pre-prandial test results that patients typically obtain.
- Exclude factors, which can falsely elevate the A1C (eg, low red cell turnover).

If the A1C is lower than expected based on the mean glucose results

- Do fingerstick blood glucose monitoring or CGM to detect nocturnal hypoglycemia, hypoglycemic unawareness, and/or frequent episodes of hypoglycemia. It is possible that blood glucose levels are low during times when testing is not being performed (such as undetected nocturnal hypoglycemia).
- Exclude factors, which can falsely decrease the A1C (eg, rapid red cell turnover).

Diabetes mellitus: management of type 2

Patient who is taking metformin for T2DM:

- if the HbA1c < 58 mmol/mol (7.5%): titrate up metformin and encourage lifestyle changes to aim for a HbA1c of 48 mmol/mol (6.5%).
- if the HbA1c rises to 58 mmol/mol (7.5%): add a second drug

General aim of management

- Reduce the incidence of macrovascular (ischaemic heart disease, stroke) and microvascular (eye, nerve and kidney damage) complications.

Risk factor modification

- **Blood pressure**
 - ⇒ target is < 140/80 mmHg (or < 130/80 mmHg if end-organ damage is present)
 - ⇒ ACE inhibitors are first-line
- **Antiplatelets**
 - ⇒ should not be offered unless a patient has existing cardiovascular disease
- **Lipids**
 - ⇒ only patients with a 10-year cardiovascular risk > 10% (using QRISK2) should be offered a statin.
 - ⇒ The first-line statin of choice is atorvastatin 20mg on

HbA1c targets

- HbA1c should be checked every 3-6 months until stable, then 6 monthly
- NICE encourage us to consider relaxing targets on '*a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes'*
- According to NICE guidelines, the HbA1c targets are now dependent on treatment:
- **Lifestyle or single drug treatment**

Management of T2DM	HbA1c target
Lifestyle alone or + metformin	48 mmol/mol (6.5%)
Includes any drug which may cause hypoglycaemia (e.g. lifestyle + sulphonylurea)	53 mmol/mol (7.0%)

Be aware that there are **other possible reasons for a low HbA1c level**, for example, **deteriorating renal function** or **sudden weight loss**.

Self-monitoring of blood glucose

- **Indications**
 - ⇒ person is on insulin or oral medication that may increase their risk of hypoglycaemia while driving or operating machinery.
 - ⇒ evidence of hypoglycaemic episodes or to confirm suspected hypoglycaemia.
 - ⇒ pregnant, or planning to become pregnant.
 - ⇒ when starting treatment with oral or intravenous corticosteroids

Lifestyle modification

- **Dietary advice**
 - ⇒ Encourage high-fibre, low-glycaemic-index sources of carbohydrate, such as fruit, vegetables, wholegrains and pulses
 - ⇒ Include low-fat dairy products and oily fish
 - ⇒ Control the intake of foods containing saturated and trans fatty acids.
 - ⇒ limited substitution of sucrose-containing foods for other carbohydrate in the meal plan is allowable, but that they should take care to avoid excess energy intake.
 - ⇒ Discourage use of foods marketed specifically at people with diabetes
- **Losing weight**
 - ⇒ Initial target weight loss in an overweight person is 5-10%
- **Physical activity**

Drug treatment

- **First line**
 - ⇒ **offer standard release metformin**
 - ⇒ **titrate up metformin** and encourage lifestyle changes to aim for a HbA1c of 48 mmol/mol (6.5%),
 - ⇒ **If gastrointestinal side effects are not tolerated, then a trial of modified release metformin would be appropriate.**
 - ⇒ If metformin is not tolerated at all then a dipeptidyl peptidase-4 inhibitor, sulfonylurea or pioglitazone would be indicated.
- **Second line**
 - ⇒ **should only add a second drug if the HbA1c rises to 58 mmol/mol (7.5%)**
 - ⇒ there is more flexibility in the second stage of treating patients (i.e. after metformin has been started) - you now have a choice of 4 oral antidiabetic agents
 - ⇒ **Second line for patient who tolerates metformin:**
 - add one of the: Sulfonylurea, Gliptin, pioglitazone or SGLT-2 inhibitor (**dual therapy**)
 - If despite the **dual therapy**, the HbA1c remains above 58 mmol/mol (7.5%) or increased then **triple therapy** with one of the following combinations should be offered:
 - ❖ metformin + gliptin + sulfonylurea
 - ❖ metformin + pioglitazone + sulfonylurea
 - ❖ metformin + sulfonylurea + SGLT-2 inhibitor
 - ❖ metformin + pioglitazone + SGLT-2 inhibitor
 - ❖ OR insulin therapy should be considered
 - ⇒ **Second line if metformin is not tolerated or contraindicated:**
 - Consider one of the: Sulfonylurea, Gliptin or pioglitazone
 - if the HbA1c has risen to 58 mmol/mol (7.5%) then **add one of the following (Dual therapy):**
 - ❖ gliptin + pioglitazone
 - ❖ gliptin + sulfonylurea
 - ❖ pioglitazone + sulfonylurea
 - if despite this the HbA1c rises to, or remains above 58 mmol/mol (7.5%) then consider insulin therapy
- **Third line**
 - ⇒ If **triple therapy** is not effective, not tolerated or contraindicated then NICE advise that we consider combination therapy with metformin, a sulfonylurea and a glucagon-like peptide1 (GLP1) mimetic if:
 - $BMI \geq 35 \text{ kg/m}^2$ and specific psychological or other medical problems associated with obesity or

- BMI < 35 kg/m² and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity related comorbidities.

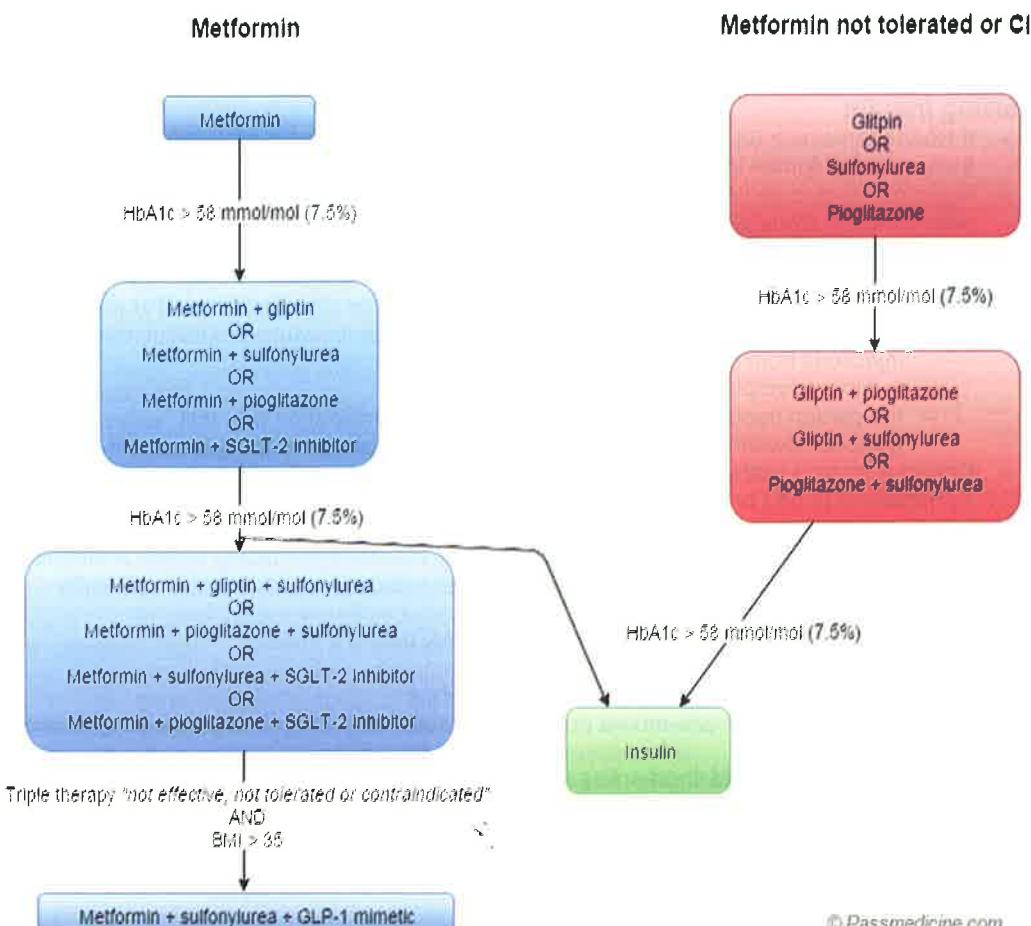
Starting insulin

- If HbA1c remains > 58 mmol/mol (DCCT = 7.5%) inspite of maximum tolerated oral therapy, then consider human insulin
- Metformin should be continued. In terms of other drugs NICE advice: '*Review the continued need for other blood glucose lowering therapies'*
- NICE recommend starting with human NPH insulin (isophane, intermediate acting) taken at bed-time or twice daily according to need.
- Consider **using insulin detemir or insulin glargine as an alternative to NPH insulin**, if:
 - the person needs assistance to inject insulin, so as to reduce the frequency of injections from twice to once daily.
 - recurrent symptomatic hypoglycaemic episodes
 - the person need twice- daily NPH injections in combination with oral glucose- lowering drugs.
- Consider starting **both NPH and short- acting insulin** (particularly if the person's HbA1c is 75 mmol/mol [9.0%] or higher), administered either: separately or as a pre-mixed (biphasic) human insulin preparation.
- Consider **pre-mixed (biphasic) preparations** that include short- acting insulin analogues, rather than pre- mixed (biphasic) preparations that include short- acting human insulin preparations, if:
 - a person prefers injecting insulin immediately before a meal or
 - hypoglycaemia is a problem or
 - blood glucose levels rise markedly after meals.
- For patients who are on **pre-mixed (biphasic) insulin and uncontrolled blood glucose**, consider:
 - further injection of short-acting insulin before meals **OR**
 - change to a basal bolus regimen with NPH insulin or insulin detemir or insulin glargine.

Special considerations

- If the patient is at risk from hypoglycaemia (or the consequences of) then a DPP-4 inhibitor or thiazolidinedione should be considered rather than a sulfonylurea
- Meglitinides (insulin secretagogues) should be considered for patients with an erratic lifestyle
- You can consider using sitagliptin or a thiazolidinedione instead of insulin if there would be employment (eg: truck driver), social, recreational, or personal issues.**
- In patients with diabetes starting thyroxine, doses of antidiabetic drugs including insulin may need to be increased.

Diabetes associated with pancreatitis is due to damage to the endocrine pancreas and associated lack of insulin. the patient's presentation: thin, with symptoms of insulinopaenia. As such, **exogenous insulin replacement is the only appropriate intervention**



Which laboratory test results would be most significantly associated with an increased incidence of cardiovascular disease in type 2 diabetics?

- Raised proinsulin levels

January 2013 exam: A taxi driver with type 2 DM, on metformin and the dose was titrated up. His HbA1c one year ago was 75 mmol/mol (9%) and is now 69 mmol/mol (8.5%). His BMI 33 kg/m². What is the most appropriate next step in management?

- Add sitagliptin (because DPP-4 inhibitors are weight neutral & no risk of hypoglycaemia)

September 2010 exam: H/O (T2DM) & bladder cancer on gliclazide and atorvastatin. A recent trial of metformin was unsuccessful due to gastrointestinal side-effects. He works as an accountant; is a non-smoker his BMI is 31 kg/m². His $\text{HbA1c} = 62 \text{ mmol/mol (7.8\%)}$ What is the most appropriate next step in management?

- Add sitagliptin (Pioglitazone is contraindicated in bladder cancer and may contribute to his obesity, he does not meet the NICE body mass index criteria of 35 kg/m².)

Biguanides (metformin)

Metformin should be titrated slowly, leave at least 1 week before increasing dose

Mechanism of action

- Inhibits mitochondrial glycerophosphate dehydrogenase (mGPD) → ↓ **hepatic gluconeogenesis** and intestinal glucose absorption
- Increases peripheral insulin sensitivity → ↑ peripheral glucose uptake and glycolysis

Indications

- type 2 diabetes mellitus
- polycystic ovarian syndrome
- non-alcoholic fatty liver disease

Action of metformin in polycystic ovary syndrome:

- metformin → ↓ **Insulin resistance** → ↑ **peripheral glucose uptake** → ↓ **hyperinsulinaemia which implicated in pathogenesis of PCOS.**

Advantages

- Glycemic efficacy: lowers HbA1c by 1.2–2% over 3 months
- Weight loss**
- No risk of hypoglycemia**
- Beneficial effect on dyslipidemia
- Reduce macrovascular complications** and death (superior to sulphonylureas and insulin in terms of macrovascular risk, e.g. myocardial infarction).

Adverse effects

- Gastrointestinal upsets are common (nausea, anorexia, diarrhoea), intolerable in 20%
 - commonly occur if not slowly titrated up.
 - The BNF advises leaving at least 1 week before increasing the dose.
 - modified release preparations reduce the risk further.
 - High dose metformin interfere with the enterohepatic circulation of bile salts, leading to **reduced reabsorption of bile salts from the ileum → chronic diarrhoea .**
- Vitamin B₁₂ deficiency**
 - Associated with long-term treatment with metformin
 - The possibility of metformin-associated B₁₂deficiency should be considered in patients on metformin who suffer cognitive impairment, peripheral neuropathy, subacute combined degeneration of the cord or anaemia.
- Lactic acidosis** with severe liver disease or renal failure
 - It is rare, although it remains important in the context of exams
 - The patients usually have severe renal impairment.
 - factors increases the risk of metformin lactic acidosis:**
 - Tissue hypoxia**, e.g. recent myocardial infarction, sepsis, acute kidney injury and severe dehydration.

- ❖ The (BNF) states that there should be a six week "cooling off" period post-MI before the commencement or recommencement of metformin.
- Contrast radiography : metformin should be discontinued on the day of the procedure and for 48 hours thereafter
- Excess alcohol intake
- Drugs: Cyclosporin, aminoglycosides, cimetidine (Metformin is excreted by the renal tubules and this process can be inhibited by cimetidine, but not the other H2 receptor antagonists).
- ⇒ The mainstay of treatment is rehydration.
- ⇒ correction of acidosis with 8.4% sodium bicarbonate.
- ⇒ Patients with resistant acidosis should be considered for haemodialysis, which also clears metformin.
- ⇒ Despite aggressive treatment, mortality still 50%.

High dose (> 2 gm daily) interferes with enterohepatic circulation of the bile salts (Bile salt malabsorption) → diarrhoea

Contraindications

- Chronic kidney disease:
 - ⇒ NICE recommend that the dose should be reviewed if the creatinine is > 130 mmol/l (or eGFR < 45 ml/min) (reduce those and monitor renal function every three months) and stopped if the creatinine is > 150 mmol/l (or eGFR < 30 ml/min) (stage four chronic kidney disease (CKD 4))
- Alcohol abuse is a relative contraindication → ↑ risk of lactic acidosis
- Intravenous iodinated contrast medium
- Heart failure (NYHA III and IV), respiratory failure, shock, sepsis
- Alcoholism

Sulphonylureas

Mechanism of action

- Block ATP-sensitive potassium channels (K_{ATP}) of the pancreatic β cells → depolarization of the cell membrane → calcium influx → insulin secretion

Side effects

- Life-threatening hypoglycemia; increased risk with the following :
 - ⇒ Age over 65 years
 - ⇒ Simultaneous intake of CYP2C9 inhibitors (e.g., amiodarone, trimethoprim, fluconazole)
 - ⇒ Patients with renal failure
 - ⇒ more common with long acting sulphonylureas such as chlorpropamide and glyburide (glibenclamide).
- Weight gain
- syndrome of inappropriate ADH secretion (SIADH)
- bone marrow suppression
- liver damage (cholestatic)
- photosensitivity
- Hematological changes: granulocytopenia, hemolytic anemia

- Chlorpropamide & tolbutamide → disulfiram-like reaction **following alcohol intake (alcohol intolerance)**.
 - ⇒ **alcohol intake** with Chlorpropamide & tolbutamide → inhibits aldehyde dehydrogenase (the enzyme responsible for the metabolism of acetaldehyde) → accumulation of toxic acetaldehyde → disulfiram-like effect (a drug used to treat alcoholism) → (**facial flushing**, erythema, paraesthesia of the extremities, nausea and vomiting, tachycardia, and hypotension).

Contraindications

- Pregnancy and breast feeding
- Severe cardiovascular comorbidity
- Severe liver and kidney failure
- Obesity
- Beta blockers (can mask hypoglycemic symptoms while lowering serum glucose levels)

The combination of beta-blockers and hypoglycemia should be avoided:

- Beta-blockers may mask the warning signs of hypoglycemia (e.g., tachycardia) and decrease serum glucose levels even further.

Agents

- Glibenclamide**
 - ⇒ long-acting sulfonylurea
 - ⇒ associated with a greater risk of hypoglycaemia, therefore, should be avoided in the elderly, and shorter-acting alternatives, such as gliclazide or tolbutamide, should be used instead
 - ⇒ Renally excreted: **renal impairment** → ↑ risk of hypoglycaemia
- Gliclazide**
 - ⇒ intermediate half-life of around 11 hours.
 - ⇒ causes less hypoglycemia than other sulfonylureas.
 - ⇒ extensively metabolised within the liver by **CYP2C9**. Renal clearance accounts for only 4% of total drug clearance. In CKD stage 1, 2, 3 (eGFR > 30 mL/min) gliclazide can be used safely. in patients with severe CKD → reduced dose can be used
 - ⇒ **gliclazide action can be potentiated predominantly by two mechanisms:**
 - Displacement of the drug from plasma proteins to give free (unbound) drug - some agents such as **aspirin** can do this, and
 - Interference with the hepatic metabolism of the drug.(e.g fluconazole)
- Glipizide**
 - ⇒ metabolized by the liver into inactive metabolites and therefore, renal insufficiency does not affect the drug's clearance.
 - ⇒ **the best choice of sulfonylureas in a patient with renal impairment** (no need for dose adjustment).
- Chlorpropamide**
 - ⇒ has a higher side effect profile
 - ⇒ may produce a syndrome of inappropriate anti-diuretic hormone (ADH) secretion.

Sulphonylurea provide **microvascular benefits**, but **NO benefit was demonstrated for macrovascular outcomes** (cardiovascular disease), in contrast to metformin.

Sulphonylurea overdoses:

In **sulphonylurea overdoses**, if the patient remains **hypoglycaemic despite infusion of sufficient glucose**, consider administration of **octreotide** (a somatostatin analogue which lowers insulin levels and thus raised blood glucose)

Meglitinides

Meglitinides - stimulate insulin release - good for erratic lifestyle

Meglitinides (nateglinide and repaglinide) → increase postprandial insulin release specifically

Agents

- Repaglinide
- Nateglinide

Action → closure of the β -cell K⁺-ATP channel.

- Short-acting insulin secretagogues
- Blockage of ATP-sensitive potassium (K_{ATP}) channels of the pancreatic beta cells → depolarization of the cell membrane → calcium influx → insulin secretion
- Act like sulphonylureas but have a weaker binding affinity and faster dissociation from the SUR1 binding site of the pancreatic channel.

Indications

- useful for post-prandial hyperglycaemia or an **erratic eating schedule**, as patients take them shortly before meals

Advantages

- The shorter action of duration result in less weight gain compared to sulphonylureas.
- Nateglinide is useful **for shift workers and patients who tend to fast for a period of time** because doses can be skipped when meals are missed. In these patient groups there may be a lower incidence of hyperglycaemia.
- Repaglinide can be used even in CKD stages 4 and 5 without dose reduction.

Adverse effects

- weight gain and hypoglycaemia (less so than sulphonylureas)

Thiazolidinediones (glitazones, insulin sensitizers)

Mechanism of action: Peroxisome Proliferator Activated Receptor (PPAR) gamma agonists → increase peripheral insulin sensitivity

Glitazones are agonists of PPAR-gamma receptors, reducing peripheral insulin resistance

A major function of peroxisomes is beta-oxidation of fatty acids

(PPAR- γ) agonists increase the metabolism of free fatty acids

Agents

- Pioglitazone
- Rosiglitazone: was withdrawn in 2010 following concerns about cardiovascular side-effect profile.

Pioglitazone metabolism

- mainly by **CYP2C8** cytochrome P450 enzyme pathway

Mechanism of action

- **Agonists** to the **peroxisome proliferator-activated receptor-gamma (PPAR-gamma)** receptor → ↑ transcription of genes involved in glucose and lipid metabolism → ↑ levels of adipokines such as adiponectin and insulin sensitivity → ↑ storage of fatty acids in adipocytes, ↓ **products of lipid metabolism (e.g., free fatty acids)** → ↓ **free fatty acids in circulation** → ↑ glucose utilization and ↓ hepatic glucose production.
 - ⇒ Metformin also boosts insulin sensitivity, but **pioglitazone has more effect on peripheral insulin resistance.**

PPAR-gamma receptor

- **an intracellular nuclear receptor.**
- Its natural ligands are free fatty acids
- it is thought to control adipocyte differentiation and function.
- **activated by free fatty acids** and thiazolidinediones such as pioglitazone.

Indications

- may be considered as monotherapy in patients with severe renal failure and/or contraindications for insulin
- **NICE guidance advice that:** only continue **thiazolidinediones** if there is a reduction of > 0.5 percentage points in HbA1c in 6 months

Advantages

- Glycemic efficacy: lowers HbA1c by 1% in 3 months
- Favorable effect on lipid metabolism: ↓ triglyceride, ↓ LDL, ↑ HDL
- No risk of hypoglycemia
- **associated with the lowest rate of secondary beta-cell failure.** Sulfonylureas are associated with the highest rate

Side effects

- ↑ Risk of heart failure
- ↑ Risk of bone fractures (**osteoporosis**). due to **reduced osteoblast activity** → **reduced bone mineral density.**
- Fluid retention and edema
 - ⇒ **the risk of fluid retention is increased if the patient also takes insulin**, or other drugs that cause fluid retention (for example, **NSAIDs, calcium antagonists**)
- Weight gain
- Rosiglitazone: ↑ risk of cardiovascular complications like cardiac infarction or death
- **Bladder cancer**
- liver impairment: monitor LFTs

Contraindications

- Congestive heart failure (NYHA III or IV)
- Liver failure
- Pioglitazone: history of bladder cancer or active bladder cancer; macrohematuria of unknown origin

Thiazolidinediones are associated with an increased risk of bladder cancer

Pioglitazone may cause fluid retention

Insulin: Basics

Structure

- Insulin is a peptide hormone, composed of 51 amino acids. It is a dimer of an A-chain and a B-chain, which are linked together by disulfide bonds.

Production

- Insulin is produced in the pancreatic beta cell by proteolytic cleavage from pro-insulin resulting in **c-peptide** which is secreted together with **insulin in a 1:1 molar ratio**.

Secretion

- Insulin is stored in secretory granules
- Released by beta cells **as a result of increased intracellular calcium**.
- **Released in pulses about every 9-13 minutes.**
 - ⇒ **This pulsing release mechanism** is important because it is thought that this keeps cells sensitive to insulin.
 - ⇒ **this is one of the first things that disappears when insulin sensitivity disappears.**
- Secreted in response to hyperglycaemia

C-peptide

- a protein cleaved from proinsulin when it is activated.
- has a longer half-life than insulin, and thus is a useful measure of insulin secretion (it is more accurate than measuring insulin itself).
- The level of this can be measured in the urine.

Insulin and C peptide are ↑ in insulinoma and sulfonylurea use, whereas exogenous insulin lacks C-peptide.

Functions

- Insulin binds to insulin receptors (a type of **tyrosine kinase receptor**) located in various tissues in the body → acts as an **anabolic hormone** in target tissues (e.g., liver, skeletal muscle, adipose tissue).
- **Carbohydrate metabolism**
 - ⇒ **Stimulate Glycogenesis** (glycogen synthesis from glucose by glycogen synthase, and glycogen branching enzyme. Triggered by high serum insulin concentrations.) in muscle and liver
 - ⇒ **Stimulate Glycolysis** (converts glucose to pyruvate and produces ATP and NADH as byproducts.) in adipose and muscle
 - ⇒ **Inhibits Glycogenolysis** (breakdown of glycogen by glycogen phosphorylase)
 - ⇒ **Inhibits Gluconeogenesis** (produces glucose from noncarbohydrate substances such as amino acids, triglycerides, and glycerol.) (**Insulin inhibit pyruvate carboxylase which used in gluconeogenesis**)
 - ⇒ Inhibits Production and release of glucagon
- **Lipid metabolism**
 - ⇒ **Stimulate Lipid synthesis and triglyceride storage in adipose tissue**
 - ⇒ **Inhibits Lipolysis** (breakdown of lipids)
 - ⇒ **Inhibits Ketogenesis** (production of ketone bodies by HMG-CoA synthase).

- Protein metabolism
 - ⇒ Stimulate Protein synthesis in muscle tissue
 - ⇒ Stimulate Uptake of amino acids
 - ⇒ Inhibits Proteolysis
- Increases cellular uptake of potassium (via stimulation of Na⁺/K⁺ ATPase pump)

Insulin therapy

Insulin types

- Rapid-acting insulin analogues (Aspart, Lispro, Glulisine)
 - ⇒ Onset: 5 mins
 - ⇒ Peak: 1 hour
 - ⇒ Duration: 3-5 hours
 - ⇒ Reduces the chance of between-meal hypoglycaemia.
 - ⇒ Useful for reducing postprandial hypoglycaemia because their profile is more in keeping with physiological insulin release.
 - ⇒ If there is a pre-lunch hyperglycaemia, that means there is a significant post-breakfast peak in glucose levels. As such, the best management → breakfast time injection of rapid acting insulin.
- Short-acting insulins (Actrapid, Humulin S)
 - ⇒ Onset: 30 mins
 - ⇒ Peak: 3 hours
 - ⇒ Duration: 6-8 hours
 - ⇒ may be used as the bolus dose in 'basal-bolus' regimes
 - ⇒ "Standard insulin" for lowering blood glucose levels in an acute setting
 - ⇒ Intravenous therapy available
- Intermediate-acting insulins (Isophane [NPH])
 - ⇒ Onset: 2 hours
 - ⇒ Peak: 5-8 hours
 - ⇒ Duration: 12-18 hours
 - ⇒ NICE guidelines advise that, in general, a humane isophane insulin is the first-line recommended insulin in type 2 diabetic.
- Long-acting insulins (Determin, Glargine)
 - ⇒ Onset: 1-2 hours
 - ⇒ Peak: Flat profile
 - ⇒ Duration: Up to 24 hours
 - ⇒ The main advantage → Reduced nocturnal hypoglycaemia
 - ⇒ might be useful in someone who struggles to inject a twice a day NPH insulin to reduce the frequency of injections to once a day (e.g. someone who requires assistance to inject from a carer or district nurse).
 - ⇒ suitable for providing a basal level of insulin which attempts to mimic the normal physiological state.
 - ⇒ In which situations does insulin glargine have the clearest advantage over isophane?
 - In patients with type-1 diabetes who have significant nocturnal hypoglycaemia on isophane
 - ⇒ NICE only recommends use of insulin glargine in patients who have significant hypoglycaemia on isophane insulin
 - ⇒ Detemir is the only long-acting insulin that is soluble in the bottle as well as under the skin, possibly allowing for more consistent absorption.

- ⇒ Detemir can be administered with other forms of insulin, unlike insulin glargine, which cannot be mixed with other insulins or IV fluids due to its acid vehicle.
- ⇒ Degludec a long-acting insulin.
 - Onset: ~1 hour
 - Half-life elimination: ~25 hours (has the highest half-life)
 - Time to peak: 9 hours

Rapid-acting insulins are your favorite GAL (Glulisine, Aspart, Lispro).

Degludec

A patient with recurrent admissions for DKA secondary to missing doses can be started on degludec to reduce readmission rate.

Degludec has a much higher half-life than Detemir and therefore maintains a basal insulin level when the patient omits or forgets doses. This can prevent DKA.

Intravenous insulin is the optimal management of high blood sugar in acute myocardial infarction.

Insulin prescription

- Starting dose
 - ⇒ The guidelines recommend starting with either morning or evening long-acting insulin, or with bedtime intermediate acting insulin.
 - ⇒ 0.2 U/kg or a flat dose of 10 U is the recommended starting dose for intermediate acting insulin.
- Targets
 - ⇒ Fasting and pre-prandial glucose levels → 4-7 mmol/L .
 - ⇒ Post-prandial glucose levels : less than 10 mmol/L.
 - ⇒ In hospitalised patients the Joint British Diabetes Societies for Inpatient care (JBDS) suggest a target blood glucose of 6-10mmol/L
- Monitoring
 - ⇒ If patients are not using insulin, sulphonylureas or glinides (repaglinide or metformin), then the ADA/EASD consensus does not recommend self-monitoring of blood glucose levels.
 - ⇒ Once daily long-acting insulin taken at night is monitored using pre-breakfast fasting glucose measurements. If fasting levels are in range yet the HbA_{1c} is elevated, post-prandial monitoring is recommended.
- Dose adjustment
 - ⇒ Pre-prandial glucose: Mainly affected by the basal insulin dose
 - ⇒ Postprandial glucose is mainly affected by meal intake and prandial insulin dose.
 - ⇒ At least three consecutive, self-monitored fasting glucose readings should be used to adjust doses (i.e. three days minimum between dose adjustments).
 - ⇒ Up-titration
 - increase 2 U of insulin every three days until fasting glucose is in the target range of 3.9-7.2 mmol/L. If the fasting plasma glucose is >10 mmol/L, → up titration schedule of 4 U every three days can be used.
 - ⇒ Down-titration
 - Reduce insulin dose in steps of 20% if hypoglycaemia occurs.
- Insulin in renal failure
 - ⇒ The dose of exogenous insulin is reduced 25% when eGFR is 10-50 mL/min and 50% when eGFR is < 10 mL/min

the most appropriate initial insulin regime for young patient after being diagnosed with new onset Type1 DM → Meal time Actrapid and insulatard at night.

Insulin side-effects

- Hypoglycaemia
- Weight gain
- Hypokalemia
- Lipodystrophy at the injection site
 - ⇒ typically presents as atrophy of the subcutaneous fat
 - ⇒ can be prevented by rotating the injection site

Mixtard- associated nocturnal hypoglycemia

- This is because the insulatard component of the Mixtard peaks about 6 h after it has been given. This, along with some residual actrapid activity, gives an excess of insulin in the middle of the night, leading hypoglycaemia.
- **Split evening insulin so take actrapid before evening meal and insulatard before bedtime**

Hypoglycaemic episodes which occur during the day in a patient takes a basal bolus insulin regime of long-acting insulin (Insulatard®) and short- acting insulin (Actrapid®) with each meal:

- the most appropriate next step → Refer for Dose Adjustment For Normal Eating education (DAFNE)
- the next step after DAFNE, should hypos persist, would be **continuous glucose monitoring**, to learn more about fluctuations in serum blood glucose over the course of the day.
- those patients who have problems with **nocturnal hypoglycaemia** → changing insulatard to insulin glargine

What is the most appropriate initial advice with respect to adjusting prandial insulin dose?

- **1 unit of insulin per 10 grams of dietary carbohydrate**

Glucagon-like peptide-1 (GLP-1)

Incretins increase insulin release and decrease glucagon secretion from the pancreas. DPP-IV metabolizes GLP. Inhibiting DPP-IV maintains high levels of GLP.

GLP-1 : Site of synthesis → Small intestinal L cells

Incretin effect

- Oral glucose load → ↑ glucagon-like peptide-1 (GLP-1), **produced by the L-cells of the ileum** → ↑ **insulin release** (more than if the same load is given intravenously), ↓ **glucagon secretion, slow gastric emptying** (↑ feeling of satiety, ↓ weight) - this known as the **incretin effect**.
- This effect is largely mediated by GLP-1 and is known to be decreased in T2DM.

Glucagon-like peptide-1 (GLP-1)

- Production

- ⇒ glucagon-like peptide-1 (GLP-1), a hormone **produced by the L-cells of the ileum** in response to an oral glucose load

- Effects in glucose homeostasis

- ⇒ **Glucose-dependent stimulation of insulin secretion**
- ⇒ Reduction of gastric emptying
- ⇒ Reduction of inappropriate glucagon secretion
- ⇒ Weight loss

- Regulation of GLP-1

- ⇒ Increasing GLP-1 levels, either by:
 - administration of an analogue (glucagon-like peptide-1, GLP-1 mimetics, e.g. exenatide) **OR**
 - inhibiting its breakdown (dipeptidyl peptidase-4 ,DPP-4 inhibitors - the gliptins), is therefore the target of two recent classes of drug.

GLP is a confusing misnomer: Glucagon raises glucose and FFA levels. GLP decreases glucagon.

Glucagon-like peptide-1 (GLP-1) analogs

Exenatide = Glucagon-like peptide-1 (GLP-1) mimetic

Exenatide causes vomiting

Agents: Exenatide, Liraglutide

- **Liraglutide VS Exenatide**

- ⇒ Liraglutide is **given once a day** (long-acting) whereas Exenatide is given **twice daily** (**has a half-life of around 2.5 hours**)

- ⇒ **Liraglutide can be used in renal impairment** with an estimated glomerular filtration rate [eGFR] as low as 30 mL/min/1.73 m². Exenatide are cleared via **renal excretion** and is therefore **not recommended in patients with an eGFR < 30**.

Mechanism of action

- Incretin effect: Oral glucose load → ↑ glucagon-like peptide-1 (GLP-1), **produced by the L-cells of the ileum** → ↑ insulin release (**more than if the same load is given intravenously**), ↓ glucagon secretion, slow gastric emptying (↑ feeling of satiety, ↓ weight).

- **GLP-1 agonists (Incretin mimetic drugs)** → ↑ GLP-1 levels → ↑ insulin secretion, ↓ glucagon secretion, slow gastric emptying (↑ feeling of satiety, ↓ weight)
- **Metabolic effects**
 - ⇒ increase insulin secretion
 - ⇒ inhibit glucagon secretion.
 - ⇒ inhibits glucose production in the liver
 - ⇒ slows gastric emptying → Suppresses appetite

Indications

- NICE state that: Consider adding exenatide to metformin and a sulfonylurea if:
 - ⇒ **BMI ≥ 35 kg/m²** in people of European descent **and** there are problems associated with high weight, **or**
 - ⇒ **BMI < 35 kg/m²** and insulin is unacceptable because of **occupational implications** or weight loss would benefit other comorbidities.

Advantages

- Improve glycaemic control: lowers HbA1c by 0.5–1.5% over 3 months
- No risk of hypoglycemia
- Promote weight loss (≈ 6% weight loss over a 6 month period).

Administration

- NICE like patients to have achieved a **1% reduction in HbA1c (11 mmol/mol)** and **3% weight loss after 6 months** to justify the ongoing prescription of GLP-1 mimetics.

Adverse effects

- nausea and vomiting (the major adverse effect).
- Acute **pancreatitis** in some patients.

The preferred pathway for glucose management according to the NICE guidelines is to add insulin to the combination of metformin and a sulphonylurea. However, **where weight is of particular concern (BMI >35), exenatide may be considered as an alternative. It can also be used where insulin would interfere with a patient's occupation.**

When to choose exenatide as an alternative to insulin or sulphonylurea as first choice add-in options to metformin?

- morbid obesity
- **or risk of hypoglycaemia, (eg : HGV drivers)**

Current NICE guidance suggests the use of GLP-1 mimetics **only if BMI is above 35 and there are specific medical or psychological problems associated with high body weight.**

Sign guidelines 2017: For individuals with **type 2 diabetes** and established cardiovascular disease, **GLP-1 receptor agonist therapies with proven cardiovascular benefit (currently liraglutide)** should be considered.

Dipeptidyl peptidase-4 (DPP-4) inhibitors (gliptins)

Gliptins = Dipeptidyl peptidase-4 (DPP-4) inhibitors

Agents

- Vildagliptin, Sitagliptin, Saxagliptin, Linagliptin and Alogliptin

Action

- Incretin effect:** Oral glucose load → ↑ glucagon-like peptide-1 (GLP-1), **produced by the L-cells of the ileum** → GLP-1 degradation via the enzyme DPP-4 → end of the GLP-1 effect.
- DPP-4 inhibitors (Incretin mimetic drugs)** bind to the GLP-1 receptors **inhibiting the DPP-4 that breaks down GLP-1 → ↑ GLP-1 levels → ↑ insulin secretion, ↓ glucagon secretion, slow gastric emptying** (↑ feeling of satiety, ↓ weight)

Indications

- Can be considered as monotherapy in patients who are intolerant of or have contraindications to metformin, or other glucose-lowering agents.
 - ⇒ e.g. **linagliptin** might be a good choice as **initial therapy** in a patient with **chronic kidney disease** or who is at particularly high risk for hypoglycemia.
- Only recommended as **second-line therapy with metformin if patients are at significant risk of hypoglycaemia** or its consequences (e.g. older patients, those working at heights or heavy machinery, isolated patients) or if a sulphonylurea is not tolerated or contraindicated.
- can be considered as add-on drug therapy for patients who are inadequately controlled on metformin, a thiazolidinedione, sodium-glucose co-transporter-2 (SGLT2) inhibitor, or a sulfonylurea.
- NICE guidelines suggest that a DPP-4 inhibitor might be preferable to a thiazolidinedione if further weight gain would cause significant problems, a thiazolidinedione is contraindicated or the person has had a poor response to a thiazolidinedione
- NICE guidelines recommend:** continue DPP-4 inhibitor only if there is a reduction of > 0.5 percentage points in HbA1c in 6 months.

Advantages

- Oral preparation
- Well tolerated with no increased incidence of hypoglycaemia
- Do not cause weight gain
- We can use them all in CKD but with dose adjustment (**Only linagliptin does not need dose adjustment in any stage of CKD**)
- Linagliptin is preferred in patients with chronic kidney disease [eGFR] <30 mL/min/1.73 m²

Side effects

- GI disturbance** (nausea, flatulence, diarrhoea and constipation) (because DPP-4 inhibitor delays gastric emptying).
- Acute pancreatitis** (insufficient data) - still under investigation but is to be discontinued in the event of pancreatitis.
- Saxagliptin associated with increased incidence of heart failure.**
- Increased risk of upper respiratory tract infections.

Sodium-glucose cotransporter 2 inhibitors (gliflozins)

Empagliflozin has been shown to reduce cardiovascular mortality

Examples

- Include canagliflozin, dapagliflozin and empagliflozin

Mechanism of action

- reversible inhibition of SGLT-2 in the proximal convoluted tubule of the kidney → ↓ glucose reabsorption → glycosuria and polyuria.

Indications

- Empagliflozin or canagliflozin may play a role in patients with overt cardiovascular diseases (CVD) or heart failure not reaching glycemic goals with metformin and lifestyle modifications
- may have a role as a third agent in those who cannot or will not take insulin, when full doses of metformin and a sulfonylurea have not produced satisfactory metabolic control, or in patients in whom risk of hypoglycemia is high (frail, older adults) or in whom avoidance of weight gain is a priority.

Advantages

- Glycemic efficacy: lowers HbA1c by 0.6% over 3 months
- Promotes weight loss (modest calorie spillage into the urine)
 - therefor it is better than gliptins in obese patient who does not achieve control by metformin
- ↓ Blood pressure (Sodium loss → fall in BP)
- ↓ Risk of cardiovascular mortality in patients with type 2 DM and cardiovascular disease
- Reduce uric acid, which may over the longer term reduce nephropathy progression
- Do not usually cause hypoglycemia

Adverse effects

- Recurrent infections due to glucosuria
 - Recurrent urinary infections (↑ glucose in the urine (Glycosuria) → predispose to bacterial growth)
 - Genital infection (Vulvovaginal candidiasis): contra-indicated in patients with recurrent thrush.
 - Necrotizing fasciitis of the perineum
- Diabetic ketoacidosis (patients may present with euglycaemic ketoacidosis)
 - SGLT-2 inhibitors → ↑glucagon, → ↑lipid oxidation → ↑risk of ketoacidosis.
- Increased risk of bone fracture
 - SGLT-2 inhibitors → ↑PTH → ↑bone turnover → ↑ risk of bone fracture.
 - SGLT-2 inhibitors → ↑ fibroblast growth factor (FGF-23) → ↓vitamin D → ↑ ↓bone mineralisation.
- Acute kidney injury
- Dehydration → weight loss, orthostatic hypotension
- Increased total cholesterol, (both HDL and LDL)
- ↑ Risk of lower limb amputation: Empagliflozin is preferred rather than canagliflozin. Canagliflozin found to be associated with increased risk of lower limb amputation and fractures.

Sign guidelines (November 2017): In individuals with type 2 diabetes and established cardiovascular disease, SGLT2 inhibitors with proven cardiovascular benefit (currently empagliflozin and canagliflozin) should be considered.

Contraindications

- Renal Impairment: eGFR <30 mL/minute/1.73 m²: Use is contraindicated.
- Recurrent urinary tract infections (e.g., in patients with anatomical or functional anomalies of the urinary tract)

Alpha-glucosidase inhibitors

Overview

- These are **acarbose**, **miglitol** and voglibose.
- Not usually used as first-line therapy, because of modest efficacy and poor tolerance.

Mechanism of action

- Inhibit the upper gastrointestinal enzymes (alpha-glucosidases) that convert complex polysaccharide carbohydrates into monosaccharides and thereby slow absorption of glucose and reduce postprandial blood glucose concentration.

Advantages

- They may be used as part of a combination regimen in people who consume high-carbohydrate diets and have high postprandial glucose levels.
- Reduction in risk of new onset type 2 diabetes and **cardiovascular events**.

Side effects

- Abdominal pain, flatulence and diarrhea (Using glucosidase inhibitors is like making a person lactose intolerant).
 - ⇒ Mechanism of diarrhoea: Alpha-glucosidase inhibitors → block glucose absorption → the sugar remains in the bowel → bacteria eat the glucose, and cast off gas and acid.

Diabetic ketoacidosis (DKA): Overview

Epidemiology

- Approximately 25% of patients with type 1 diabetes will first present in diabetic ketoacidosis

Pathophysiology

- Osmotic diuresis and hypovolemia**
 - ⇒ Insulin deficiency → hyperglycemia → hyperosmolality → osmotic diuresis and loss of electrolytes → hypovolemia
- Metabolic acidosis with increased anion gap**
 - ⇒ Insulin deficiency → ↑ lipolysis → ↑ free fatty acids → hepatic ketone production (ketogenesis) → ketosis → bicarbonate consumption (as a buffer) → high anion gap metabolic acidosis

- ⇒ Lack of insulin → ↑ cortisol, catecholamines and **glucagon** → ↑ fatty acid metabolism → ↑ **beta-hydroxybutyrate** → **acetoacetate** → **urine ketone**
- ⇒ **Insulin withdrawal** → **initial acute rise in glucagon concentrations** → **Hepatic glucose production** rises rapidly over the first 2 – 4 hours reaching a plateau after around 4 hours.

• Intracellular potassium deficit

- ⇒ Insulin deficiency → hyperosmolality → K⁺ shift out of cells + lack of insulin to promote K⁺ uptake → intracellular K⁺ depleted → total body K⁺ deficit despite normal or even elevated serum K⁺ (**Total body potassium is reduced by up to 500 mmol**)

What is the primary cause of ketoacidosis in type 1 diabetes?

- **Lipolysis**

Causes

- **Precipitating factors leading to diabetic ketoacidosis (DKA) are:**
 - ⇒ Infection (30-40%) The most common precipitating factor
 - ⇒ **Non-compliance with treatment (25%)**
 - ⇒ Newly diagnosed diabetes (10-20%)
 - ⇒ Alterations to insulin dose (13%)
 - ⇒ Myocardial infarction (< 1%)
- **The drugs implicated in precipitating diabetes as well as diabetic ketoacidosis.**
 - ⇒ **atypical antipsychotics such as olanzapine**
 - ⇒ thiazide diuretics
 - ⇒ beta sympathomimetics, and
 - ⇒ steroids.

Features

- abdominal pain
- polyuria, polydipsia, dehydration
- Kussmaul respiration (deep hyperventilation)
- Acetone-smelling breath ('pear drops' smell) (Fruity odor)
- **serum sodium is falsely low** due to the osmotic load of glucose.
- Blood count:
 - ⇒ Platelet secretory activity is often increased in DKA, but aggregation decreased.
 - ⇒ Neutrophil count is also commonly raised and correlates with ketone body levels, so does not necessarily imply underlying infection.

Diagnostic criteria: All of these must be present to make the diagnosis:

- The 'D' – a blood glucose of >11.0 mmol/L or known to have diabetes mellitus
- The 'K' a capillary or blood ketone of >3.0 mmol/L or significant ketonuria (2+ or more)
- The 'A' – a bicarbonate of <15.0 mmol/L and/or venous pH <7.3

Association

A raised amylase in the absence of frank pancreatitis is common in patients with diabetic ketoacidosis (DKA), No specific management is required, and amylase falls with rehydration and control of blood glucose.

Very high glucose artificially drops sodium level → Pseudohyponatremia

Cause of hyperkalemia → transcellular shift of potassium out of the cell in exchange for hydrogen.

Cause of ↓ total body K stores → excess loss of solutes with water in the urine.

Cause of hypokalemia during DKA treatment → insulin drives potassium into cells with glucose.

Assessment of severity : presence of one or more of the following may indicate **severe**

DKA (suggest intensive care admission):

- GCS < 12
- Oxygen saturation <92% on air
- Systolic blood pressure <90 mmHg
- Tachycardia (>100) or bradycardia (< 60 bpm)
- pH < 7
- Blood ketone > 6 mmol/L
- Bicarbonate < 5 mmol/L
- Anion gap >16 mmol/l. [Anion Gap = ($\text{Na}^+ + \text{K}^+$) – ($\text{Cl}^- + \text{HCO}_3^-$)]. Normal values are 8-12 mEq/L.
- **Potassium < 3.5 mmol/L on admission**

Differential diagnosis

- **Alcoholic ketoacidosis**
 - ⇒ Ketoacidosis without a raised glucose in a person with alcoholism is virtually diagnostic of alcoholic ketoacidosis.
 - ⇒ a careful history needs to be taken to differentiate it from euglycaemic DKA.
 - ⇒ If alcoholic ketoacidosis is suspected, then β -hydroxybutyrate should be measured and not urine ketones, because acetoacetate production can be suppressed in alcoholic ketoacidosis.
- **Starvation ketosis**
 - ⇒ ↓ carbohydrate intake → ↓insulin secretion, → lipolysis and ketosis.
 - ⇒ because it arises over a prolonged period, → renal compensation → acid base and electrolyte disturbances are often minimal

Diabetic ketoacidosis (DKA): Management

Fluid replacement

- **Calculate fluid deficit**
 - ⇒ mild to moderate DKA (indicated by a blood pH of 7.1 or above) → 5% fluid deficit.
 - ⇒ severe DKA (indicated by a blood pH below 7.1) → 10% fluid deficit.
 - ⇒ Most patients with DKA are deplete **around 5-8 litres**.
- **Calculate maintenance fluid requirement**
 - ⇒ if they weigh less than 10 kg, give 2 ml/kg/hour
 - ⇒ if they weigh between 10 and 40 kg, give 1 ml/kg/hour
 - ⇒ if they weigh more than 40 kg, give a fixed volume of 40 ml/hour.
- **Choose appropriate fluids**
 - ⇒ Use 0.9% sodium chloride until the plasma glucose is below 14 mmol/litre. **If the glucose falls below 14.0 mmol/L:**
 - commence 10% glucose given at 125 ml/ hour alongside the 0.9% sodium chloride solution, so that the insulin infusion can be continued at a sufficient rate to clear ketones (for example, 6 units/hour, monitored for effect).

- In addition consider reducing the rate of intravenous insulin infusion to 0.05 units/kg/hr.
- ⇒ All fluids (except any initial bolus) administered with 40 mmol/litre potassium chloride unless they have renal failure.

- **Rate of fluid replacement**

- ⇒ **JBDS example of fluid replacement regime for patient with a systolic BP on admission 90mmHg and over:**

Fluid	Volume
0.9% sodium chloride 1L	1000ml over 1st hour
0.9% sodium chloride 1L with potassium chloride	1000ml over next 2 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 2 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 4 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 4 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 6 hours

- ⇒ **Slower infusion may be indicated in young adults** (aged 18-25 years → risk of cerebral oedema), elderly, heart or kidney failure.

Fluid deficit in DKA

- ❖ Assume a 5% fluid deficit in children and young people in **mild or moderate DKA** (indicated by a blood **pH of 7.1 or above**)
- ❖ Assume a 10% fluid deficit in children and young people in **severe DKA** (indicated by a blood **pH below 7.1**)

Insulin

- **Insulin type**

- ⇒ Soluble infusion → intravenous infusion at **0.1 unit/kg/hour**.
- ⇒ If patient normally takes **long acting insulin analogue (Lantus, Levemir)** continue **at usual dose and time**. In those newly diagnosed, then a long acting basal insulin should be commenced, at a dose of 0.25 units/Kg subcutaneously once daily.

- **Best time for starting** → NICE recommend to start insulin infusion **1–2 hours after beginning intravenous fluid therapy**

- **Rate of infusion (fixed rate insulin regime, not a sliding scale).**

- ⇒ 0.1 unit/kg/hr based on estimate of weight
- ⇒ 50 units human soluble insulin (Actrapid or Humulin S) made up to 50 ml with 49.5 ml 0.9% sodium chloride solution (i.e. 1 unit /ml).
- ⇒ Once the glucose drops to <14 mmol/L then in addition to **adding a 10% dextrose infusion** consider **reducing the rate of intravenous insulin infusion to 0.05 units/kg/hr** to avoid the risk of developing hypoglycaemia and hypokalaemia
- ⇒ **Insulin infusion rate should only be increased if blood ketones are not falling at >0.5 mmol/h, venous bicarbonate not increased by 3.0mmol/L/hour or capillary blood glucose not reduced by 3.0mmol/L/hour.**

Correction of hypokalaemia

- As a result of both acidosis and insulin deficiency there is a **total body potassium deficit of up to 1000 mmol**.
- rehydration, insulin replacement and correction of acidosis resulting in further potassium loss with restoration of urine flow
- hypokalemia is a major cause of death in ketoacidosis.

- JBDS potassium guidelines

Potassium level in first 24 hours (mmol/L)	Potassium replacement in mmol/L of infusion solution
Over 5.5	Nil
3.5-5.5	40
Below 3.5	Senior review as additional potassium needs to be given

Other treatment

- Bicarbonate

- The role of bicarbonate in DKA is controversial. Generally not recommended.
- The acidosis usually corrects itself once the fluid and electrolyte balance is restored.
- There is no evidence to support bicarbonate use in a patient with a pH greater than 7.0.
- Intravenous bicarbonate should be given if the blood pH is lower than 6.9.
- In practice for DKA, sodium bicarbonate is only really considered in the peri-arrest situation.

- Low-molecular weight heparin

- DKA increased risk of venous thromboembolism because of volume depletion, hyperglycaemia and their decreased conscious level.

Monitoring

- Blood glucose should be assessed every hour but testing for urine ketones can be performed every 4 hours.

Assessment of treatment

- Targets

- Reduction of the blood ketone concentration by 0.5mmol/L/hour
- Increase the venous bicarbonate by 3.0mmol/L/hour
- Reduce capillary blood glucose by 3.0mmol/L/hour

- If these targets rates are not achieved:

- always check the insulin infusion pump malfunction (the correct insulin residual volume is present)
- then the FRIII rate should be increased by 1 unit/hr increments hourly until the targets are achieved.

- Expected time of DKA resolution

- It is unusual for DKA not to have resolved by 24 hours with appropriate treatment

- Indicators of DKA resolution: Resolution of DKA is defined as:

- pH > 7.3 units.
- bicarbonate > 15.0mmol/L; and
- blood ketone level < 0.6mmol/L (rather than < 0.3mmol/L), in order to avoid restarting the FRIII if the ketone level rebounds upon discontinuation of the FRIII

- Unreliable indicators of acidosis resolution

- Glucose level is not an accurate indicator of resolution of acidosis in ketoacidosis, so the acidosis resolution should be verified by venous gas analysis.
- Do not rely on bicarbonate alone to assess the resolution of DKA due to the possible hyperchloraemia secondary to large volumes of 0.9% sodium chloride infusion.
 - ↑↑ 0.9% sodium chloride infusion → ↓HCO₃ → hyperchloraemic metabolic acidosis → difficulty in assessing whether the ketosis has resolved.

- hyperchloraemic acidosis may cause renal vasoconstriction → oliguria.
- ⇒ Do not rely on urinary ketone clearance to indicate resolution of DKA, because these will still be present when the DKA has resolved.

Euglycaemic DKA

- **Definition:** DKA in people known to have diabetes but where the glucose is normal, or not particularly raised.
- **Causes**
 - ⇒ partial treatment of DKA prior to admission
 - ⇒ use of the sodium-glucose cotransporter (SGLT) inhibitor drugs (e.g. dapagliflozin, canagliflozin, empagliflozin)
- **Treatment:** treated in exactly the same way as hyperglycaemic DKA.
 - ⇒ 1) Initiate glucose 10% straight away at 125 ml/hr because the glucose is < 14 mmol/L
 - ⇒ 2) Begin with 0.1 units/kg/hr insulin rate
 - ⇒ 3) If glucose falling despite 10% glucose reduce to 0.5 units/kg/hr to avoid hypoglycaemia

SCE-question sample-mrcpuk.org :

The **non-improvement of the patient's clinical status** and biochemical findings suggest that the **metabolic acidosis is due to another reason** such as **sepsis**. The finding of a **raised lactate concentration** will provide further insights.

Typical deficits in DKA in adults:

- Water - 100ml/kg
- Sodium - 7-10mmol/kg
- Chloride - 3-5mmol/kg
- Potassium - 3-5mmol/kg

Resolution of DKA is defined as:

- pH > 7.3 units.
- bicarbonate > 15.0mmol/L; and
- **blood ketone level < 0.6mmol/L (rather than < 0.3mmol/L)**, in order to avoid re-starting the FRIII if the ketone level rebounds upon discontinuation of the FRIII

At which time, a patient can be converted back to subcutaneous insulin?

- **After Resolution of DKA**

Metabolic treatment targets

- Reduction of the blood ketone concentration by 0.5 mmol/L/hour
- Increase the venous bicarbonate by 3.0 mmol/L/hour
- Reduce capillary blood glucose by 3.0 mmol/L/hour
- Maintain potassium between 4.0 and 5.5 mmol/L

If these targets are not achieved, then the fixed rate intravenous insulin infusion (FRIII) rate should be increased by 1 unit/hr increments hourly until the targets are achieved.

Complications of DKA and its treatment

- **Cerebral oedema**
 - ⇒ The risk is highest in paediatric (1%) and adolescent patients and is rarer in adults.
 - ⇒ **Mechanism**
 - Exact pathogenic mechanism remains unknown – multifactorial
 - ↑glucose → ↑osmolar gradient results in water shift from the intracellular fluid (ICF) to the extracellular fluid (ECF) space and contraction of cell volume.
 - Correction with insulin and I.V fluids → rapid reduction in osmolarity → reversal of the fluid shift → cerebral edema.
 - ⇒ **Features**
 - headache
 - agitation or irritability
 - unexpected fall in heart rate
 - increased blood pressure.
 - deterioration in level of consciousness
 - abnormalities of breathing pattern, for example respiratory pauses
 - oculomotor palsies
 - pupillary inequality or dilatation.
 - ⇒ **Treatment**
 - mannitol (20%, 0.5–1 g/kg over 10–15 minutes) or hypertonic sodium chloride (3% over 10–15 minutes) to induce osmotic fluid shifts.
 - urgent treatment should be started when cerebral oedema is suspected and **not be delayed whilst awaiting imaging.**
- Thromboembolism
- Acute respiratory distress syndrome
- Arrhythmias secondary to hyperkalaemia/iatrogenic hypokalaemia
- Acute kidney injury (AKI): Transient AKI may occur in up to 50% of adults.
- **Recovering DKA are at risk of hypophosphataemia**
 - ⇒ weakness following treatment for DKA.
 - ⇒ often arises as a side effect of insulin with cells forming ATP and taking up free phosphate to achieve this.

Prognosis

- **The mortality rate associated with the modern management of DKA → 1-2%**
- Specifically, mortality relates to cerebral oedema.

(SCE-question samples.mrcpuk.org)

A 26-year-old woman with **DKA**. After 24 hours of treatment with intravenous fluids, potassium and insulin, her normal subcutaneous insulin regimen was resumed. However, she felt nauseated and there was a concomitant increase in **blood ketones to 3.5 mmol/L (<0.3)**, random plasma glucose: **7.3 mmol/L**. What is the most appropriate next step in management?

- **start glucose 10% with fixed-rate intravenous insulin**
 - ⇒ A fixed-rate insulin infusion is recommended for faster resolution of DKA.
 - ⇒ If the blood glucose is below 14 mmol/L, it is necessary to administer intravenous infusion of 10% glucose in order to avoid hypoglycaemia and permit the continuation of fixed-rate intravenous insulin.

Hypoglycaemia

Definition

- In patients with diabetes: generally described as $\leq 3.9 \text{ mmol/L}$ ($\leq 70 \text{ mg/dL}$).
- It can be defined as "mild" if the episode is self-treated and "severe" if assistance by a third party is required.

Counter-regulatory responses in patients with hypoglycaemia and threshold for symptoms

- There is considerable variability in the serum glucose level at which a person will experience symptoms of hypoglycemia. Usually occurred by the time serum glucose concentration is $< 2.8 \text{ mmol/L}$ (50 mg/dL).
- **Response mechanisms against hypoglycaemia in healthy patients:**
 - ⇒ **The first response is → insulin release inhibition.** This occurs when plasma glucose reaches approximately 4 mmol/L .
 - ⇒ The second response is → counterregulatory hormone release (glucagon, adrenaline, noradrenaline, cortisol, and growth hormone). Occurs when glucose drops to $3.6\text{-}3.9 \text{ mmol/L}$.
- **Recurrent hypoglycemia in diabetic patients** → hypoglycemia-associated autonomic failure (HAAF) → changes in the counterregulatory response (e.g., decreased epinephrine release) → lower glucose threshold needed to trigger symptoms → asymptomatic hypoglycemia (for this reason, the initial symptom of hypoglycemia in patients with HAAF is often confusion.)

Epidemiology

- between 30 to 40 % of patients with type 2 diabetes experience symptomatic hypoglycemia.
- **The prevalence of severe hypoglycaemia is similar in patients with type 2 diabetes receiving insulin for more than 5 years to that in patients with type 1 diabetes**

Causes

Diabetic patients: relative overdose of insulin or a noninsulin drug is the most common cause.

- **Insulin-related**
 - ⇒ **Insulin excess or noninsulin drugs (e.g., sulfonylureas, meglitinides)**
 - ⇒ **Increased sensitivity to insulin (weight loss, ↑ activity/exercise)**
 - ⇒ **Decreased insulin clearance (renal failure)**
- **Glucose-related** (missed meals, Exercise)
- **Acute illness (sepsis, organ failure)**

Nondiabetic patients

- **Endogenous hyperinsulinism or IGF (insulinoma, Gastric bypass surgery (late dumping syndrome))**
- **Exogenous hyperinsulinism** (self-administration of insulin/sulphonylureas)
- **Critical illness (sepsis, organ failure)**
- Liver failure
- Hormone deficiencies (hypopituitarism, adrenal insufficiency)
- Alcohol
- **Autoimmune causes**
 - ⇒ Insulin autoimmune syndrome (IAS)
 - ⇒ Anti-insulin receptor autoantibodies: Usually associated with autoimmune diseases like Sjögren syndrome and SLE.
- **Drugs that cause hypoglycemia**
 - ⇒ **Nonselective beta blockers**

- ⇒ Antimalarial drugs: quinine, chloroquine
- ⇒ Antibiotics: sulfonamides, trimethoprim-sulfamethoxazole, fluoroquinolones
- ⇒ Antifungal drugs: pentamidine, oxaline
- ⇒ Analgesics: indomethacin, propoxyphene/dextropropoxyphene
- ⇒ Antihypertensive drugs: **ACE-inhibitors** → improve insulin sensitivity.
- ⇒ Antiarrhythmics: cibenzoline, disopyramide
- ⇒ **Low dose aspirin** → ↓ prostaglandin synthesis → stimulate beta cell
- ⇒ Others: IGF-1, lithium, mifepristone, heparin, 6-mercaptopurine

Consider factitious disorder in patients with access to insulin and other diabetes medications (e.g., healthcare professionals), for whom there is no other obvious explanation for hypoglycemia.

Beta blockers can mask signs of hypoglycaemia.

Features

- Neurogenic/autonomic
 - ⇒ **Increased sympathetic activity:** tremor, pallor, anxiety, tachycardia, sweating, and palpitations
 - ⇒ **Increased parasympathetic activity:** hunger, paresthesias, nausea, and vomiting
- Neuroglycopenic
 - ⇒ Agitation, confusion, behavioral changes
 - ⇒ Fatigue
 - ⇒ Seizure, focal neurological signs
 - ⇒ **Nocturnal hypoglycaemia → vivid dreams** → REM sleep disruption → daytime weakness and somnolence.
 - ⇒ Somnolence → obtundation → stupor → coma → death

Diagnosis → Whipple triad:

- ⇒ **Low plasma glucose concentration**
- ⇒ **Signs or symptoms consistent with hypoglycemia**
- ⇒ **Relief of symptoms when plasma glucose increases after treatment**

Standard work-up for hypoglycaemia:

- Laboratory (not test-strip) blood glucose measurement
- Insulin and C-peptide levels **taken during the hypoglycaemic attack**
 - ⇒ Hypoglycaemia + hyperinsulinaemia → insulin is the cause of hypoglycaemia.
 - ⇒ External insulin does not contain C-peptide, which is released from pancreatic islet with endogenous insulin.
 - ⇒ ↑ Insulin + ↓ C-Peptide → insulin abuse
 - ⇒ ↑ Insulin + ↑ C-Peptide → endogenous hyperinsulinism (e.g insulinoma, sulphonylurea)
- **Sulphonylurea level** (serum or urine)
- Liver function tests to rule out significant liver dysfunction
- Blood alcohol and alcohol history
- Cortisol levels, with or without Synacthen testing
- Chest X-ray to exclude occult malignancy

Work-up for hypoglycaemia is not indicated in two occasions

- If the Whipple triad is not confirmed, no further workup is indicated.
- Hypoglycemia in diabetic patients is almost always due to acute illness and/or medications (e.g., insulin) and further workup is generally not indicated.

If both C-peptide and insulin are raised → Suggests endogenous insulin secretion.
 • Request a plasma sulfonylurea screen is the most appropriate next step, and depending on the result of this, further investigation may be required.

↑ Insulin with ↓ C-Peptide level points to a diagnosis of insulin abuse → Exogenous insulin administration (as the C peptide is released with endogenous insulin).
 C-Peptide level ↑ with Sulfonylurea abuse

Management

- For patient who are able to swallow:
 - ⇒ Oral glucose 15–20 g (**Fast-acting carbohydrates** such as glucose tablets, candy, or juice)
 - Chocolate is not recommended as it contains **fat which shown to slow the absorption of quick acting carbohydrate.**
 - ⇒ Repeat capillary blood glucose measurement 10–15 minutes later. If it is still less than 4.0mmol/L, repeat step 1 (no more than 3 treatments in total).
 - ⇒ If blood glucose remains less than 4.0mmol/L after 30–45 minutes or 3 cycles, Consider: 150–200ml of 10% I.V glucose over 15 minutes
 - ⇒ Once blood glucose is above 4.0mmol/L and the patient has recovered, give a **long acting carbohydrate** (e.g. Two biscuits, One slice of bread/toast, 200–300ml glass of milk, Normal meal if due).
- For patient who are unable to swallow (e.g. Glasgow Coma Scale Score < 13):
 - ⇒ If intravenous access can be obtained.
 - I.V glucose:
 - ❖ 10% or 20% glucose solutions are preferred options:
 - ⇒ give 75–100ml of 20% glucose over 15 minutes. Repeat capillary blood glucose measurement 10 minutes later. If it is still less than 4.0mmol/L, repeat.
 - ⇒ give 150–200ml of 10% glucose over 15 minutes. Repeat capillary blood glucose measurement 10 minutes later. If it is still less than 4.0mmol/L, repeat
 - ❖ 50% intravenous dextrose is not recommended by Joint British Diabetes Societies (JBDS): (hyperosmolarity → risk of extravasation injury, venous endothelium destruction and phlebitis).
 - ⇒ if no intravenous access can be obtained → **Glucagon** (1 mg intramuscularly)
 - Glucagon acts on the liver by **Activates adenylate cyclase** → ↑ glycogenolysis and gluconeogenesis → rapid correction of hypoglycaemia

Hypoglycaemic symptoms with normal blood glucose level

- Adults who have poor glycaemic control may start to experience symptoms of hypoglycaemia above 4.0mmol/L.
- adults who are experiencing hypoglycaemia symptoms but have a blood glucose level greater than 4.0mmol/L – treat with a small carbohydrate **snack only** e.g. 1 medium banana, a slice of bread or normal meal if due. (diabetologists-abcd.org.uk)

MRCPUK-part-1-September 2011 exam: An 18-year-old girl is admitted with hypoglycaemia (RBS: 1.9 mmol). her father who has type 2 DM describes a number of similar episodes. Insulin 15 mg/ml (6-10 mg/ml) Proinsulin 22% (22-24%) C-peptide 0.15 nmol/l (0.2-0.4 nmol/l). What is the most likely diagnosis? **Insulin abuse** (The raised insulin with low c-peptide level points to a diagnosis of insulin abuse. C-peptide levels would be raised in a patient following sulfonylurea abuse)

Hypoglycaemic episodes after regular exercise in patient who takes BD mixed insulin:

- the most appropriate next step in his management is → transfer to a basal bolus regime where he can alter his short acting insulin dose just prior to planning exercise.

Diabetes mellitus: early morning hyperglycemia

Overview

- The most common causes of morning hyperglycemia are nocturnal growth hormone secretion and hypoinsulinaemia.
- There is no evidence to support the existence of **Somogyi effect** (nocturnal hypoglycemia leading to a surge of counterregulatory hormones, leading to hyperglycemia in the morning). The opposite is typically found, ie, patients with morning hyperglycemia typically have high, not low, blood glucose concentrations at night.

Dawn phenomenon

- Definition:** A physiological increase of **growth hormone (GH)** levels in the early morning hours **stimulates hepatic gluconeogenesis** and leads to **early-morning hyperglycemia**
- Diagnosis:** measurement of nocturnal blood glucose → **normal nocturnal glycemia**, with **early-morning hyperglycemia**
- Treatment:** Long-acting insulin dose may be given later or increased under careful glycemic control.

Hypoglycaemia unawareness (HU)

Definition

- Hypoglycemia unawareness (HU) is defined as onset of neuroglycopenia before the appearance of autonomic warning symptoms.

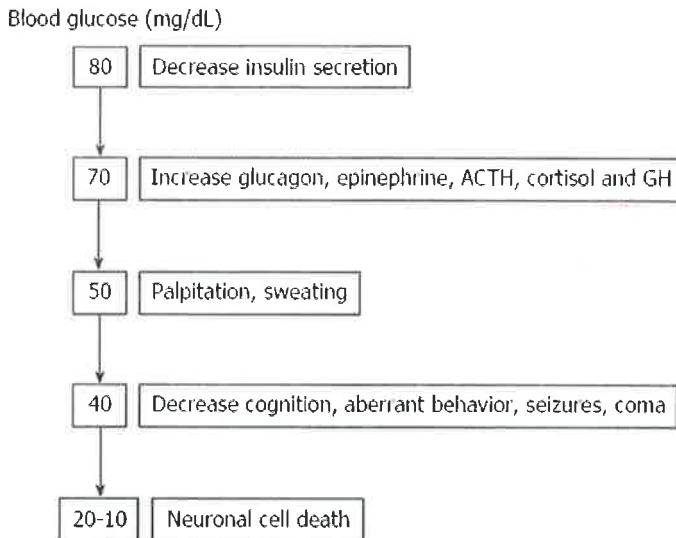
Incidence

- Occurs in approximately 40% of people with type 1 diabetes mellitus (T1DM) and with less frequency in T2DM.

Mechanism

- Recurrent hypoglycaemia → hypoglycemia-associated autonomic failure (HAAF) → failure of counter-regulatory hormones → inability to recognise impeding hypoglycaemia by symptoms.
- Impaired awareness of the symptoms of plasma glucose levels below 3 mmol/litre is associated with a significantly increased risk of severe hypoglycaemia.
- more common in patients with **intensively controlled diabetes** of long duration, leading to **recurrent hypoglycaemia**.
- Alcohol inhibits gluconeogenesis, decreases peripheral hypoglycaemic responses and impairs perception of symptoms of hypoglycaemia.**

Symptoms and signs associated with progressive hypoglycemia



Treatment

- Optimizing insulin treatment, flexible insulin therapy using basal–bolus regimens → Avoidance of hypoglycemia
- avoid hypoglycaemia in adults with type 1 by offering insulin pump and real-time continuous glucose monitoring.
- In recurrent severe hypoglycaemia that has not responded to other treatments refer to islet cell transplantation.
- NICE advise to **avoid** relaxing individualised blood glucose targets to address impaired hypoglycaemia awareness → use the recommended targets
- The patient demonstrating hypoglycemia unawareness is required to stop driving for 3 months after a second episode of hypoglycaemia.**

Hyperosmolar hyperglycaemic state (HHS)

Pathophysiology

- Severe hyperglycemia → ↑ serum osmolality → osmotic diuresis → severe dehydration
- In general, **there is enough insulin in patients with type 2 diabetes to suppress ketogenesis**, but insufficient to prevent hyperglycaemia and the hepatic resistance to glucagon.

Overview

- Occurs most commonly in elderly people with type 2 diabetes
- Infection is the commonest precipitating factor (80%).
- Mortality is higher than DKA (5% to 15%).

Features

- Osmotic features : Polyuria, polydipsia,
- Dehydration: dry mucous membranes, poor skin turgor, hypotension.
- Acute cognitive impairment (lethargy, disorientation, stupor) is common

Diagnostic criteria

- Hypovolaemia
- Hyperglycemia (≥ 30 mmol/L)
- ↑ Serum osmolality (> 320 mOsm/kg)
- Normal serum pH and ketones (pH > 7.3 , bicarbonate > 15 mmol/L and no significant ketonaemia < 3 mmol/L)

Management

- Fluids**
 - Fluid losses in HHS are estimated to be between 100 - 220 ml/kg (e.g. 10-22 litres in an individual weighing 100 kg).
 - The fluid of choice is 0.9% sodium chloride (NaCl).
 - Only switch to 0.45% (NaCl) if the osmolality is not declining despite adequate positive fluid balance. An initial rise in sodium is expected and is not itself an indication for hypotonic fluids.
 - Fluid replacement alone with 0.9% sodium chloride solution will result in falling blood glucose.
 - IV fluid replacement should aim to achieve a positive balance of **3-6 litres by 12 hours and the remaining replacement of estimated fluid losses within the next 12 hours**.
- Insulin**
 - Low dose IV insulin (0.05 units/kg/hr) should only be commenced once the blood glucose is no longer falling with IV fluids alone OR immediately if there is significant ketonaemia (3β -hydroxy butyrate greater than 1 mmol/L or urine ketones greater than 2+) (e.g. mixed DKA / HHS picture).
- Potassium**
 - Patients with HHS are potassium deplete, decreased intracellular K+ (normal or increased serum K+).
 - less common problem in HHS than DKA but monitoring and replacement are essential
 - Potassium should be replaced or omitted as required
 - If potassium level in first 24 hr (mmol/L) → No potassium replacement
 - If K : 3.5 – 5.5 → 40 mmol/L
 - If K below 3.5 → senior review as additional potassium required
- Prophylactic anticoagulation:** low molecular weight heparin (LMWH)

Targets

- The fall in blood glucose should be no more than 5 mmol/L/hr
- The rate of fall of plasma sodium should not exceed 10 mmol/L in 24 hours.
- Rapid changes of serum osmolarity are dangerous and can result in cardiovascular collapse and central pontine myelinolysis (CPM).
- Measure or calculate osmolality ($2\text{Na}^+ + \text{glucose} + \text{urea}$) frequently to monitor treatment response

Complication

- Thrombotic events such as myocardial infarction, stroke or peripheral arterial thrombosis.
- Cerebral oedema, seizures secondary to rapid reduction in serum osmolality.
- Rapid correction of hyponatraemia, may lead to cerebral pontine myelinolysis

Diabetes mellitus: hypertension management

Antihypertensive therapy is the single intervention most likely to reduce the overall risk of both microvascular and macrovascular events.

- Lipid lowering therapy → prevent macrovascular events, but has no effect on microvascular events.
- Lowering HbA_{1c} only prevent → microvascular events.

First-line antihypertensive drug

- For most diabetics regardless the age → ACE inhibitor.
- For African or Caribbean family origin: ACE inhibitor plus either a diuretic or a generic calcium-channel blocker.
- For a woman for whom, there is a possibility of becoming pregnant → calcium-channel blocker
- Because ACE-inhibitors have a renoprotective effect in diabetes they are the first-line antihypertensives recommended
- If an ACE inhibitor or ARB cannot be used, alternative first-line agents include calcium channel blockers and diuretics. However, in patients with severely increased albuminuria, nondihydropyridine agents (eg, diltiazem, verapamil) are generally preferred over dihydropyridine drugs (eg, amlodipine, felodipine), since nondihydropyridine calcium channel blockers can reduce albuminuria.
- The routine use of beta-blockers in uncomplicated hypertension should be avoided, particularly when given in combination with thiazides, as they may cause insulin resistance, impair insulin secretion and alter the autonomic response to hypoglycaemia.

Targets: NICE recommend the following blood pressure (BP) targets for type 2 diabetics:

- If end-organ damage (e.g. renal disease, retinopathy) $< 130/80 \text{ mmHg}$
- If NO end-organ damage $< 140/80 \text{ mmHg}$

ACE inhibitors are first-line for hypertension in diabetics, irrespective of the patients age

Post prandial pain in diabetics

Macrovascular atherosclerosis in diabetes → Post prandial pain

- Diabetes, especially Type 2 diabetes, is associated with macrovascular disease.
- Smoking is a further risk factor for macrovascular atherosclerosis.
- **After a meal splanchnic blood flow is increased. If the mesenteric artery is occluded the lack of blood flow to the bowel will produce ischaemic type pain.**

Diabetic retinopathy

Definition

- Diabetic retinopathy is the retinal consequence of chronic progressive diabetic microvascular leakage and occlusion.

Epidemiology

- The most common cause of visual impairment and blindness in adults aged 25-65 years-old.
- **About 80% of patients with type I diabetes will have retinopathy 10 years after presentation. By contrast, in type II diabetes, where the time of onset is uncertain, up to 25% of patients will have retinopathy at the time of diagnosis.**
- Features of retinopathy usually do not appear in patients with type 1 diabetes for up to 5 years following diagnosis.

Causes of rapid worsening of diabetic retinopathy

- **Pregnancy**
- **Rapid improvement in blood glucose**
 - ⇒ suddenly dropped glucose levels → retinal artery vasoconstriction → rapid deterioration of retinopathy.
- The risk of diabetic retinopathy significantly increased in smokers with type 1 diabetes while **significantly decreased in smokers with type 2 diabetes** (a meta-analysis published in 2018).

Pathogenesis

- Hyperglycaemia → ↑ retinal blood flow & abnormal metabolism in the retinal vessel walls → damage to endothelial cells & **pericytes**
 - ⇒ Endothelial dysfunction → ↑ vascular permeability → exudates (seen on fundoscopy).
 - ⇒ **Pericyte dysfunction** → predisposes to the formation of **microaneurysms**.
 - ⇒ Retinal ischaemia → **production of growth factors** → Neovascularization

Which factor has been shown to have an important role in regulating retinal capillary blood flow?

- **Contractile action of pericytes.**
- DM → ↓ retinal pericytes (normally **contractile action of pericytes regulates retinal capillary blood flow**) → disordered blood flow regulation → ↑ retinal blood flow → ↑ shear stress on the vessel walls → **retinopathy**.

The most likely cause of blurred vision in a newly diagnosed diabetic who was previously fit and well is → Osmotic changes in the lens.

Features

- Asymptomatic until very late stages of disease
- Visual impairment
- Progression to blindness

Classification

The earliest sign of diabetic retinopathy is the presence of microaneurysms on fluorescein angiography.

Recently a new classification system has been proposed, dividing patients into those with non-proliferative diabetic retinopathy (NPDR) and those with proliferative retinopathy (PDR):

Traditional classification	New classification
Background retinopathy <ul style="list-style-type: none"> • microaneurysms (dots) • blot haemorrhages (≤ 3) • hard exudates 	Mild NPDR <ul style="list-style-type: none"> • 1 or more microaneurysm Moderate NPDR <ul style="list-style-type: none"> • microaneurysms • blot haemorrhages • hard exudates • cotton wool spots, venous beading/looping and intra-retinal microvascular abnormalities (IRMA) less severe than in severe NPDR Severe NPDR <ul style="list-style-type: none"> • <u>blot haemorrhages and microaneurysms in 4 quadrants</u> • venous beading in at least 2 quadrants • IRMA in at least 1 quadrant
Pre-proliferative retinopathy <ul style="list-style-type: none"> • cotton wool spots (soft exudates; ischaemic nerve fibres) • > 3 blot haemorrhages • venous beading/looping • deep/dark cluster haemorrhages • more common in Type I DM, treat with laser photocoagulation 	

Non-Proliferative Diabetic Retinopathy (NPDR)

- **Subtypes**
 - ⇒ **Mild NPDR**
 - 1 or more microaneurysm
 - ⇒ **Moderate NPDR**
 - Microaneurysms
 - blot haemorrhages
 - hard exudates
 - cotton wool spots, venous beading/looping and intra-retinal microvascular abnormalities (IRMA) less severe than in severe NPDR
 - ⇒ **Severe NPDR**
 - blot haemorrhages and microaneurysms in 4 quadrants
 - venous beading in at least 2 quadrants
 - IRMA in at least 1 quadrant
- **Management**
 - ⇒ regular observation
 - ⇒ if severe/very severe consider panretinal laser photocoagulation

Proliferative retinopathy

- **Features**

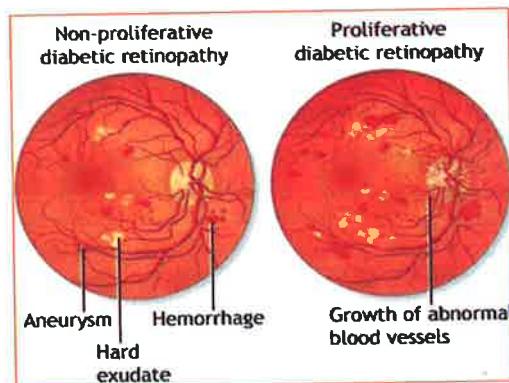
- ⇒ More common in Type I DM, 50% blind in 5 years
- ⇒ **Normal visual acuity is seen in proliferative retinopathy**
- ⇒ **Retinal neovascularisation (new vessels)**- may lead to vitreous haemorrhage

- **Management**

- ⇒ **Urgent referral to an ophthalmologist (seen within one week)**
- ⇒ laser photocoagulation: **90% effective in preventing loss of vision in type 1 diabetes.**
- ⇒ Intravitreal anti-vascular endothelial growth factor (VEGF) injection
- ⇒ If severe or vitreous haemorrhage: vitreoretinal surgery.

Maculopathy

- More common in Type II DM
- May occur in all stages of NPDR and PDR
- **Macular oedema is a common form of maculopathy:** Occurs when there is abnormal leakage and accumulation of fluid in the macula from damaged blood vessels in the nearby retina.
- **Mechanism:** Retinal vessel microangiopathy → **blood leaks** → retinal hemorrhages → **retinal infiltration with lipids and fluid** → macular edema
- **Features**
 - ⇒ Macular oedema, Hard **exudates** and macular ischemia.
 - ⇒ The exudates can be arranged in a **ring (circinate exudates)** surrounding a point of capillary leakage.
- **Diagnosis:** Can be shown on **fluorescein angiography**
- **Management**
 - ⇒ check visual acuity
 - ⇒ responds to laser treatment at the point of leakage.
 - ⇒ If there is a change in visual acuity then intravitreal vascular endothelial growth factor (VEGF) inhibitors.



Cotton wool spots (CWS) is a pre-proliferative feature: represent infarcts of the nerve fibre layer of the retina.

Diabetic Eye Screening Programme (NHS-2015)

- Screening for diabetic retinopathy is offered to all people aged 12 and over with type 1 or type 2 diabetes.
- Intervals between screening tests
 - For diabetics at low risk of sight loss: one year to two years.
 - For those at high risk of sight loss: one-year

Treatment

- Glycaemic control**
 - Achievement of target HbA1c of 47.54 mmol/mol (6.5%) would be associated with significantly reduced progression of retinopathy.
 - Should be done gently and gradually (**over several weeks**) because suddenly drop glucose levels → retinal artery vasoconstriction → rapid deterioration of retinopathy.
- Hypertensive control has been shown to be more effective than glycaemic control at reducing progression.**
- Indications for emergency referral to ophthalmologist:**
 - sudden loss of vision
 - rubeosis iridis
 - pre-retinal or vitreous haemorrhage
 - retinal detachment.
- Indication for urgent referral to the ophthalmologist (seen within one week)**
 - Hard exudates in the macular region** (evidence of clinically significant macular oedema)
 - proliferative retinopathy
 - Vitreous haemorrhage**

Prognosis

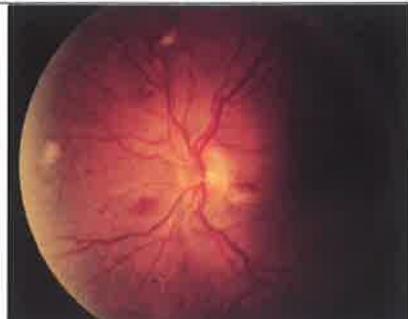
- The percentage of irreversible loss of vision within 5 years if not treated:**
 - 3% in those with background retinopathy
 - 20% for those with exudative
 - 30% for those with pre-proliferative,
 - 50% for those with proliferative retinopathy.**

Asymmetric diabetic retinopathy

Asymmetric DM Retinopathy → suspect ocular ischaemia (carotid artery disease)

- Asymmetric diabetic retinopathy** should always raise the suspicion that there is some other cause of ocular ischaemia on the worst-affected side, such as unilateral or asymmetrical carotid artery disease → do **Carotid Doppler**.

Hypertensive retinopathy



The presence of flame and blot haemorrhages, cotton wool spots and blurring of the optic disc margins are typical of the retinal changes that are seen in advanced hypertensive retinopathy. Whilst some of these findings are also observed in diabetic eye disease (e.g. dot and blot haemorrhages, cotton wool spots), the absence of other features (e.g. hard exudates, venous beading) should alert the clinician to other possible diagnoses.

Diabetic retinopathy during pregnancy

Diabetic retinopathy may rapidly deteriorate during pregnancy; therefore needs dilated fundoscopy or photography every trimester (3 monthly).

- Because of the increased risk of progression of the disease in pregnancy, conception should be delayed till the ocular disease is treated and stabilized and good diabetic control.

Diabetic neuropathy

Mechanism of neuropathy in diabetes (Nerve ischemia)

- Diabetes damages small blood vessels, which supply the nerve leads to nerve ischaemia.

Overview

- Chronic hyperglycaemia damages small blood vessels, which supply the nerve leads to nerve ischaemia.
- Distal symmetric polyneuropathy is the most common form.
- Sensory nerves are affected more than motor so often **reflexes remain intact**.
- Diabetic peripheral neuropathy** usually goes in parallel with retinopathy and nephropathy.
- It is also slowly progressive and affects mainly the spinothalamic pathway.
- The most distal portion of the longest nerves is affected first.

Risk factors

- poorly controlled hyperglycaemia
- prolonged duration of diabetes (e.g., >10 years)
- Older age (e.g., >70 years)
- Tall stature (longer fibres are more vulnerable to injury).
- Hypertension
- Smoking
- Dyslipidaemia with elevated triglycerides
- co-existence of multiple CVD risk factors (type 2 diabetes)

Features

- Asymptomatic (Up to 50%), but the physical examination reveals mild to moderately severe progressive **symmetric** loss of sensation in the distal lower extremities (stocking glove sensory loss)
- Pain is the most common **symptom induced by the involvement of small fibres**

- Loss of sensation → painless injuries over pressure points, most commonly on the foot, over the metatarsal heads.
- Autonomic features

Symptoms and signs of distal symmetric polyneuropathy (DSPN)

	Large, myelinated nerve fibers	Small, myelinated nerve fibers
Function	Pressure, balance	Nociception, protective sensation
Symptoms	Numbness, tingling, poor balance	Pain: burning, electric shocks, stabbing
Examination (clinically diagnostic)	Ankle reflexes: reduced/absent Vibration perception: reduced/absent 10 g monofilament (light pressure): reduced/absent Proprioception: reduced/absent	Thermal (cold/hot) discrimination: reduced/absent Pinprick sensation: reduced/absent

Large fiber involvement in neuropathy results in **reduced proprioception**, light pressure and **vibration sensation** and is the **earliest clinically identifiable** feature of peripheral sensory motor neuropathy.

Short fiber neuropathy is a later manifestation of diabetic peripheral neuropathy, with symptoms including **hyperparesthesia** and **superficial pain**. Examination findings indicative of short fiber neuropathy include **impaired thermosensation**, **reduced sweating** and a **cold foot**

Treatment: First-line: **duloxetine**, amitriptyline, gabapentin or pregabalin

- Duloxetine**
 - Action: serotonin-norepinephrine reuptake inhibitor (SNRI)
 - Duloxetine is preferred to amitriptyline because it is associated with a lower risk of urinary retention.**
 - Contraindications:**
 - history of glaucoma
 - patients already taking a serotonergic agent, such as **tramadol**, because of the associated risk of serotonin syndrome.
- Amitriptyline**
 - recommended by NICE as **second line** if duloxetine is unsuitable.
 - Contraindications:**
 - glaucoma and left bundle branch block**
- Pregabalin or gabapentin**
 - Action: voltage-gated calcium channel modulator
 - considered as second or third line monotherapy or in combination.
 - If there is renal impairment, pregabalin is preferable over gabapentin.**
- If the first-line drug treatment does not work try one of the other 3 drugs

Pharmacotherapy for painful diabetic neuropathy: Relevant comorbidities for drug selection

Drug class	Comorbidities favoring use	Comorbidities favoring avoidance
Serotonin-norepinephrine reuptake inhibitors (SNRIs) Duloxetine Venlafaxine	<ul style="list-style-type: none"> Depression Anxiety 	<ul style="list-style-type: none"> Restless legs syndrome Sexual dysfunction (for venlafaxine) Angle-closure glaucoma
Tricyclic antidepressants (TCAs) <ul style="list-style-type: none"> Amitriptyline Nortriptyline Desipramine 	<ul style="list-style-type: none"> Depression Anxiety Insomnia 	<ul style="list-style-type: none"> Cardiac disease Prolonged QTc Orthostatic hypotension Sexual dysfunction Urinary retention Angle-closure glaucoma
Gabapentinoid anticonvulsants <ul style="list-style-type: none"> Pregabalin Gabapentin 	<ul style="list-style-type: none"> Restless legs syndrome Essential tremor Insomnia 	<ul style="list-style-type: none"> Substance abuse Peripheral edema Chronic obstructive pulmonary disease

Peripheral neuropathy with H/O **glaucoma** and on **tramadol** for chronic back pain, what is the best treatment?

- Pregabalin**

Acute painful neuropathy of rapid improvement of blood glucose control

- rapid improvement of blood glucose control → Acute painful neuropathy (self-limiting)
→ Simple analgesics (paracetamol, aspirin) and local measures (bed cradles) are recommended as a first step

- Duloxetine** is the standard first line therapy for neuropathy
- Amitriptyline** is an alternative option to duloxetine if it is contraindicated; (e.g. presence of glaucoma)
- Pregabalin** is recommended either as a second line agent or in combination with amitriptyline.

MRCPUK-part-1-September 2009 exam: H/O type 2 DM and benign prostatic hypertrophy (BPH) presents with burning pain in his feet. He tried duloxetine but no benefit. What is the most suitable initial management?

- Pregabalin**
- Amitriptyline is first choice but given H/O BPH, it is better to avoid amitriptyline due to the risk of urinary retention.

Diabetic autonomic neuropathy

Features

Urogenital system	<ul style="list-style-type: none"> Erectile dysfunction (most common) Bladder dysfunction: urinary retention, incomplete bladder emptying, bladder distention, overflow incontinence, poor urinary stream
Cardiovascular system	<ul style="list-style-type: none"> Silent myocardial infarction Decreased heart variability or fixed rhythm <ul style="list-style-type: none"> ⇒ Heart rate variability during breathing of < 10 beats per minute ⇒ Heart rate increase on standing of < 15 beats per minute Orthostatic hypotension Persistent sinus tachycardia Ventricular arrhythmia
Gastrointestinal system	<ul style="list-style-type: none"> Gastroparesis <ul style="list-style-type: none"> ⇒ Delayed gastric emptying due to nonmechanical obstruction ⇒ Mostly idiopathic but also associated with diabetes mellitus and upper GI surgery ⇒ Manifested with nausea, abdominal bloating, early satiety ⇒ Increased risk of postprandial hypoglycemia ⇒ Treatment involves prokinetic agents, e.g., metoclopramide (first-line), erythromycin, domperidone. Diarrhea, constipation, incontinence
Other manifestations	<ul style="list-style-type: none"> Sweat gland dysfunction associated with heat intolerance Pupillary dysfunction Risk of hypoglycemia due to absence of hormonal counter-regulation (secretion of cortisol, glucagon, and catecholamines)

Type 2 diabetes with erratic blood glucose control or unexplained gastric bloating or vomiting → Think about a diagnosis of gastroparesis.

Diabetic amyotrophy

Leg pain, weakness and reduced knee reflexes with an impaired fasting glucose concentration suggests a diagnosis of **diabetic amyotrophy** → should be confirmed with OGTT.

Definition

- Diabetic amyotrophy is a type of diabetic neuropathy which affects the lumbosacral plexus, nerve roots and peripheral nerves, therefore known as **proximal diabetic neuropathy** and diabetic lumbosacral plexopathy. It is a mixed motor and sensory proximal neuropathy that can cause severe pain.

Epidemiology

- Relatively uncommon, affect 1% of patients
- Typically occurs in patients with type 2 diabetes mellitus that has been recently diagnosed or has been under fairly good control.

Pathophysiology

- The most likely mechanism is ischemic injury from microvasculitis leading to axonal degeneration (e.g. occlusion of the vasa nervorum of the proximal lumbar plexus and/or femoral nerve).

Differences from other types of diabetic neuropathy

- Patients usually have not had diabetes for a long time, and glycaemic dysregulation is often not severe.
 - ⇒ A diagnosis of diabetic amyotrophy leads to the discovery of underlying diabetes mellitus in one quarter to one third of cases.
 - ⇒ Long-term diabetic complications such as diabetic retinopathy and nephropathy are often absent at the time of diagnosis.

Features

- Pain is usually the first symptom, often in the thigh, hips or buttocks
- Often asymmetrical (although it can be bilateral).
- Wasting and weakness of proximal muscles (e.g. difficulty getting out of a chair)
- Weight loss
- Loss of knee reflexes
- There is often little sensory loss.
- Autonomic failure

Investigations

- EMG shows multifocal denervation in paraspinal & leg muscles.
- MRI is useful to rule out other causes of neurologic impairment, such as structural lesions of the lumbosacral plexus, brachial plexus, or spinal cord.

Prognosis

- Often self-improvement with time
- Most patients will not recover completely.

Treatment

- No treatments are proven to be effective.
- Neuropathic pain treatments include amitriptyline, gabapentin, pregabalin, or duloxetine.
- May improve with good control (**the mainstay of treatment is supportive care and transference to insulin therapy**).

Diabetic foot

Epidemiology

- 2% of patients with diabetes in the community develop new foot ulcers each year

Pathophysiology

- It occurs secondary to two main factors:
 - ⇒ **neuropathy**: resulting in loss of protective sensation (e.g. not noticing a stone in the shoe), Charcot's arthropathy, dry skin
 - ⇒ **peripheral arterial disease**: diabetes is a risk factor for both macro and microvascular ischaemia

Presentations

- Neuropathy: loss of sensation
- Ischaemia: absent foot pulses, reduced ankle-brachial pressure index (ABPI), intermittent claudication
- Complications: calluses, ulceration, Charcot's arthropathy, cellulitis, osteomyelitis, gangrene

Screening

- All diabetic patients should be screened for diabetic foot at least annually.
- **screening for ischaemia**: done by palpating for both the dorsalis pedis pulse and posterior tibial artery pulse
- **screening for neuropathy**: a 10 g monofilament is used on various parts of the sole of the foot.

Differential diagnosis

- **Venous stasis ulcers**
 - ⇒ **Mechanism**: **Venous reflux** → congestion and dilated veins, which impair the transport of fresh blood to the area.
 - ⇒ **Sites**: Typically present in the area around the ankle
 - ⇒ **Treatment**:
 - **Multi-layer bandaging** is most useful in reducing lower limb oedema and improving the chances of healing of venous ulcers.
 - **An ankle brachial pressure index (ABPI) measurement is essential before beginning bandaging**, as if there is significant arterial insufficiency, blood supply to the lower limb may be threatened.

Features

Neuropathic foot	Ischaemic foot
often warm	Cold foot
Painless or abnormal neuropathic pain.	causes rest pain
bounding pulses	nearly pulseless foot
ulceration tends to occur on the plantar surface	Ulceration tends to be painful and often presents in the heel area
It can be high arched, with toe clawing.	there is often gravity-dependent reddening of the foot, which disappears on elevation of the foot.

In about one third of patients with diabetic foot, the underlying cause is both ischemic and neuropathic.



This is a typical **neuropathic ulcer**, with callus forming the edge and a clean base.

Diabetic neuropathic arthropathy (Charcot foot)

In patients with long-standing diabetes and peripheral neuropathy, a **red, hot swollen foot** should raise suspicion of Charcot neuroarthropathy after exclude infection.

Definition

- Disrupted and damaged joint (mid-foot collapse) secondary to a loss of sensation.

Causes

- **Diabetes mellitus (The most common cause)**

Pathophysiology

- **Multifactorial, due to a combination of mechanical, neuropathic and vascular**
 - ⇒ Peripheral neuropathy (lack of pain sensation) → ↑ stress injuries to foot joints (commonly the midfoot) → Charcot process.
 - ⇒ Autonomic neuropathy → ↑ blood flow to the joint → ↑ osteoclast activity and bone turnover "washing out" of bone substance → ↑ foot susceptibility to minor trauma → destructive changes → Charcot's
- The commonest affected joints are tarso-metatarsal joint and metatarsophalangeal joint.

Features

- The foot and ankle are typically swollen, red and warm
- Midfoot arch collapse can lead to bony prominences on the plantar aspect with later pressure ulceration
- Typically, less painful than would be expected given the degree of joint disruption due to the sensory neuropathy. However, 75% of patients report some degree of pain

Diagnosis

- Infection such as osteomyelitis is important to exclude.
 - ⇒ Normal C-reactive protein and white blood cell count → make osteomyelitis unlikely
 - ⇒ Although not widely available, an **indium-labelled white cell scan** is the best way to differentiate between infective causes of this clinical presentation and Charcot's arthropathy.

- **X-ray:** plain radiographs can be normal in the early stages. later on, they show joint destruction, osteolysis, joint reorganisation and subluxation.
- MRI: in acute Charcot's arthropathy shows midfoot subchondral bone marrow edema

Management

- **Immobilisation in a plaster cast for 3–6 months is the treatment of choice.**
- Bisphosphonates : bisphosphonates → reduction in bone reabsorption → accelerate healing.
- Surgery: reserved for severe deformities

Necrobiosis lipoidica diabetorum

Definition

- A disorder of collagen degeneration with a granulomatous response, thickening of blood vessel walls, and fat deposition.

Causes

- Occurs in patients with type 1 diabetes,
- It is usually related to diabetes, but **can also occur in patients with rheumatoid arthritis**
- May precede symptoms and signs of diabetes by several months.

Epidemiology

- More common in females
- Presents in young adults or in early middle life.

Features

- Typically, painless.
- **Beginning as a patch of erythema that spreads across the shin, begins to yellow and can then ulcerate.**

Diagnosis

- Biopsy reveals granuloma formation with infiltration of lymphocytes, plasma cells and eosinophils.

Treatment

- **Topical steroids is the most appropriate treatment to the non-atrophied areas.** the areas of already atrophied skin respond poorly to steroid therapy.
- Support bandaging



Necrobiosis lipoidica diabetorum

Diabetes mellitus: DVLA

Patients on insulin may now hold a HGV licence if they meet strict DVLA criteria

If a patient has two or more episodes of severe hypoglycaemia (i.e. patient needs help to correct the hypoglycaemic episode) then they need to inform the DVLA and not drive.

Type 1 vehicles (cars, motorcycles)

- If on insulin then patient can drive a car as long as they:
 - ⇒ have hypoglycaemic awareness,
 - ⇒ not more than one episode of hypoglycaemia requiring the assistance of another person within the preceding 12 months
 - ⇒ no relevant visual impairment.
 - ⇒ Drivers are normally contacted by DVLA
- If on diet controlled alone, tablets or exenatide no need to notify DVLA.

Type 2 vehicles (lorries, HGV)

- HGV drivers can retain their license even if taking insulin, providing they are able to meet a set of criteria.
- Criteria regarding driving for patient on insulin (and also apply to patients using other hypoglycaemic inducing drugs such as sulfonylureas):

- 1) having no episodes of hypoglycaemia requiring the assistance of another person within the preceding 12 months
- 2) evidence of good glycemic control - demonstrated by review of 3months of BM readings on insulin**
- 3) close BM monitoring (at least BD)
- 4) full hypoglycaemia awareness
- 5) the ability to manage hypoglycaemia independently
- 6) no other complications of diabetes (e.g. visual field impairments.)

Hypoglycaemia (DVLA regulations)

- **Group 1 drivers who have had more than one episode of severe hypoglycaemia (requiring the assistance of another person) while awake in the last 12 months**
 - ⇒ Must not drive and must notify the DVLA.
 - ⇒ DVLA will then carry out medical enquiries before a licensing decision is made.
- **Group 2 drivers who have had more than one episode of severe hypoglycaemia**
 - ⇒ **Must not drive** and must notify the DVLA following all episodes of severe hypoglycaemia including asleep episodes.
- **Severe hypoglycaemia whilst driving**
 - ⇒ All Group 1 and Group 2 drivers must not drive and must notify the DVLA.

Impaired awareness of hypoglycaemia – ‘hypoglycaemia unawareness’

Group 1 (Car and motorcycle)	Group 2 (Bus and lorry)
<ul style="list-style-type: none"> • Must not drive and must notify the DVLA. • Driving may resume <u>after a clinical report</u> by a GP or consultant diabetes specialist <u>confirms that hypoglycaemia awareness has been regained</u>. 	<ul style="list-style-type: none"> • Must not drive and must notify the DVLA. • The licence will be refused or revoked.

- Who will inform the DVLA?
 - ⇒ the **patient should be advised to inform the DVLA themselves** rather than breaking patient confidentiality,
 - ⇒ if the patient repeatedly fails to follow this advice, then **the doctor should inform the DVLA** after telling the patient that he or she is doing so.
- **What advice should be given to a patient on insulin therapy, who developed hypoglycaemia requiring the assistance of another person in the preceding twelve months, with respect to his driving? → Discontinue driving for 1 year**

A guide for drivers with insulin treated diabetes who wish to apply for Group 2 (bus and lorry)

- No hypoglycaemic event requiring the help of another person in the last 12 months.
- must have full awareness of the symptoms of hypoglycaemia.
- must be able to show an understanding of the risks of hypoglycaemia.
- must check blood sugar levels at least twice daily, even on non-driving days and no more than 2 hours before the start of the first journey and every 2 hours while driving. This must be done using a blood glucose (sugar) meter with a memory function to measure and record blood glucose levels.

- must attend an examination every 12 months with an independent consultant specialising in the treatment of diabetes.
- must have at least 3 continuous months of readings available on the memory of the blood glucose meter(s) for the consultant/GP to inspect.

Drivers with insulin treated diabetes are advised by DVLA to:

- should check glucose less than 2 hours before the start of the first journey and every 2 hours after driving has started.
- A maximum of 2 hours should pass between the pre-driving glucose check and the first glucose check after driving has started.
- In each case if glucose is 5.0mmol/L or less, eat a snack. If it is **less than 4.0mmol/L** or feel hypoglycaemic **do not drive**.

DVLA advice on developing hypoglycaemia at times relevant to driving

- In each case if your glucose is 5.0mmol/L or less, eat a snack.
- If it is less than 4.0mmol/L or you feel hypoglycaemic do not drive.
- If hypoglycaemia develops while driving stop the vehicle safely as soon as possible.
- You should switch off the engine, remove the keys from the ignition and move from the driver's seat.
- You should not start driving again until **45 minutes** after finger prick glucose has returned to normal (at least 5.0mmol/L). It takes up to 45 minutes for the brain to recover fully.
- Your finger prick glucose level must be at least **5.0mmol/L** before returning to driving.

Jobs that are not allowed to subjects with insulin dependent diabetes

- Armed forces
- Working offshore or aboard ships
- Air pilot
- Police, Fire or driving in the post office (Traffic police driver)**
- Driving emergency vehicles
- Offshore work

If a patient has two or more episodes of severe hypoglycaemia (needs help to correct the hypoglycaemic episode) then they need to inform the DVLA and not drive. (needs to surrender their driving licence)

Insulinoma

Insulinoma is diagnosed with supervised prolonged fasting

Definition

- Insulinoma is a neuroendocrine tumor arising from beta cells of the pancreas

Overview

- Most common pancreatic endocrine tumour
- incidence of 4 cases per million/year
- commoner in women
- 10%** malignant. 90% are benign.
- 10%** have multiple tumours. ~ 90% occur as solitary tumors

- 10% may be associated with the MEN-1 syndrome (50% of patients with multiple tumours, have MEN-1)
- 90% are less than 2 cm in size.
- < 1% occur at ectopic sites (e.g., spleen).

Features

Whipple triad is required before further investigations for insulinoma:

1. hypoglycemic symptoms,
2. low blood glucose level
3. resolution of symptoms after correcting the blood glucose levels.

- Features of hypoglycaemia: **typically fasting hypoglycemia** (early in morning or just before meal). e.g. hunger, diplopia, sweating, palpitations, memory loss, seizures.
- Rapid weight gain: Patients eat in an attempt to avoid hypoglycaemia

Diagnosis

- **Insulin + C-peptide levels during a hypoglycaemic episode**
 - ⇒ hypoglycemia with inappropriately high insulin levels (hyperinsulinism)
 - ⇒ high C-peptide
 - ⇒ raised proinsulin: insulin ratio
- **Supervised, prolonged fasting (up to 72 hours)**
 - ⇒ If the patient develops symptoms, then a plasma glucose is measured and if low, insulin and C-peptide is then collected and the fast terminated.
 - ⇒ Positive if serum glucose levels remain low (< 40 mg/dL) and insulin levels remain high even after fasting for 72 hours.
 - ⇒ After a 15 h fast, the cut-off normal limits for glucose are 2.5 mmol/l and 5 mU/l for insulin.
 - ⇒ By 24 h, fasting leads to a detection rate of 78% for insulinoma. If the fast is extended to 72 h, this detection rate increases to 98%.
- **Sulphonylurea screen** to exclude possible drug administration
- Images to localize the tumor. abdominal CT with contrast.

Elevated C-peptide and proinsulin levels may also be the result of sulfonylurea use! This can be ruled out by screening serum samples for sulfonylureas.

Management

- Surgery is treatment of choice
- If surgery is not possible (unfit, refusal, inoperable tumor) → inhibitors of insulin release
→ **Diazoxide** (potassium channel activator)

Glucagonoma

Glucagon physiology

- Made by α cells of pancreas.
- Secreted in response to hypoglycemia.
- Inhibited by insulin, amylin, somatostatin, hyperglycemia.
- Functions (catabolic effects)
 - ⇒ ↑↑ gluconeogenesis from amino acid substrates.
 - ⇒ ↑↑ glycogenolysis
 - ⇒ ↑↑ lipolysis, ↑↑ amino acid oxidation , ↑↑ ketogenesis
 - ⇒ ↑↑ blood glucose
 - ⇒ ↑↑ catecholamine secretion
 - ⇒ Delays gastric emptying
 - ⇒ ↓↓ glycolysis
 - ⇒ ↓↓ pancreatic exocrine secretions.

Overview

- A neuroendocrine tumor that secrete glucagon.
- Very rare, with an annual incidence of 1 in 20 million.
- Usually solitary, and the majority are located in the distal pancreas.
- Frequently malignant.
- 50 - 80% are metastatic at presentation, so prognosis is poor.

Features

- Glucose intolerance , secondary diabetes mellitus
- Weight loss due to protein catabolism
- Chronic diarrhea
- Neuropsychiatric features
- Venous thrombo-embolism
- **Necrolytic migratory erythema**
 - ⇒ The most common symptom (found in 75% of cases)
 - ⇒ Red, blistering rash, starts as an indurated erythema, within a few days blisters will cover the surface of the skin, which then crust and heal, leaving hyperpigmented skin.
 - ⇒ Located predominantly on the face, perineum, and lower extremities, with lesions developing in one area while others are resolving.

Glucagonoma → 6 Ds

1. Decreasing weight
2. Diabetes
3. Dermatitis
4. Diarrhea
5. DVT
6. Depression.

Diagnosis

- Measure plasma glucagon levels → Elevated
- Image: CT scan

Management

- Somatostatin analogs (eg, octreotide) → improves the skin rash and diarrhoea
- Surgical cure rate is only 5% because these tumours have often metastasized on presentation.

Monogenic diabetes: Maturity-onset diabetes of the young (MODY)

Definition

- Different forms of **autosomal dominant** inherited diabetes mellitus characterized by onset of diabetes at a young age (**<25 years**) and **lack of autoantibodies**.

Epidemiology

- It is thought that around 1-2% of patients with diabetes mellitus have MODY, and around 90% are misclassified as having either type 1 or type 2 diabetes mellitus.

General features

- Subacute presentation (ketosis is not a feature at presentation).
- Mild to moderate hyperglycaemia (typically 7-14 mM).
- Absence of obesity → Absence of insulin resistance → low insulin requirement (e.g. less than 0.5 u/kg/day).
- **Strong family history of early onset diabetes.**
- Absence of autoimmune markers.

Diagnosis

- High index of suspicion (familial diabetes with autosomal dominant pattern of inheritance [≥ 3 generations], onset <25 years, nonobese, negative islet autoantibodies)
- Genetic testing: the most common mutations:
 - ⇒ hepatocyte nuclear factor-1-alpha (**HNF1A**) → **MODY type 3**
 - ⇒ glucokinase (**GCK**) → **MODY type 2**
 - ⇒ hepatocyte nuclear factor-4-alpha (**HNF4A**) → **MODY type 1**

Subtypes

- **MODY 3 (HNF1A-MODY)**
 - ⇒ the **commonest** form of MODY, **60%** of cases
 - ⇒ due to a defect in the **HNF-1 alpha** gene (hepatic nuclear factor-1)
 - ⇒ characterised by:
 - ↑HDL cholesterol levels
 - Preserved insulin sensitivity
 - Low renal threshold for glucose (glycosuria)
 - ⇒ Sulphonylureas is the initial drug of choice
 - ⇒ **MODY3 is particularly important to diagnose as many patients initially treated with insulin can in fact be managed with sulphonylurea.**
- **MODY 2 (GCK-MODY)**
 - ⇒ **Prevalence:** 20% of cases (The second commonest MODY variant after MODY3)
 - ⇒ **Mechanism:** due to a defect in the **glucokinase gene (GCK gene)**
 - Glucokinase is found in the liver and in beta cells in the pancreas. acts as a sensor, recognizing when the level of glucose in the blood rises and helping stimulate the release of insulin from beta cells to control it. In the liver,

- glucokinase helps determine when excess glucose should be taken in and converted to glycogen.
- When this gene isn't working properly the body allows the level of blood glucose to be higher than it should be.
 - ⇒ **Features:** Mild hyperglycaemia (slightly higher than normal, generally between 5.5-8mmol/l). Often picked up through routine testing (eg during pregnancy).
 - ⇒ **Treatment:** 90% of MODY2 patients are controlled on **diet therapy alone**.
 - ⇒ **Prognosis:** In contrast to all other subtypes, MODY II is **not associated with an increased risk of microvascular disease** and can be managed with diet alone, despite stable hyperglycemia and chronically elevated HbA1C levels.
- **MODY type 1 (HNF4A -MODY)**
 - ⇒ Defect in HNF-4 Alpha gene.
 - ⇒ The third commonest MODY (<10%)
 - ⇒ Beta cell defect: Reduced insulin secretory response to glucose
 - ⇒ Normal renal threshold for glucose
 - ⇒ Treatment : Sulfonylureas
- **MODY 5 (HNF1B-MODY)**
 - ⇒ **Defect in HNF-1 beta gene.**
 - ⇒ Rare
 - ⇒ **Renal cysts**
 - ⇒ Hypomagnesemia
 - ⇒ Treatment: insulin is usually necessary

Bilateral renal cysts + ↑ glucose → MODY related cyst formation

HNF4-alpha is associated with macrosomy, and with hypoglycaemia in the neonatal period. It is an uncommon form of MODY.

Latent autoimmune diabetes of adulthood (LADA)

Definition

- a variant of diabetes characterized by a late onset of type 1 (autoimmune) diabetes that is often mistaken for type 2 diabetes.

Epidemiology

- constitutes approximately 10% of patients incorrectly labelled as type 2 diabetic.

Feature

- **Features consistent with type 1 diabetes (eg: weight loss)**
- In contrast to type 2 diabetes, patients are typically younger and without an increased body habitus.
- In contrast to type 1 diabetes, insulin is not usually required in the early stages of the disease. the progression of autoimmune -cell failure is slow.

Diagnosis

- Glutamic Acid Decarboxylase (GAD) Autoantibodies test

Management

- early use of insulin may prolong beta-cell function
- a recent Cochrane review concluded that a sulphonylurea should not be the first line treatment since it may be associated with a more rapid progression to insulin dependence

Mitochondrial diabetes

Definition

- A rare variant of diabetes occurred due to mutation in the mitochondrial DNA.

Features

- Can present as type 1 or type 2 depending on the severity of insulinopenia.
- Strong familial clustering of diabetes. Although this is also seen in MODY, **mitochondrial diabetes can be discriminated from MODY by:**
 - Presence of **maternal transmission**
 - Bilateral hearing impairment** (usually precede the development of diabetes) → do audiology.

Diagnosis

- Mitochondrial diabetes is suspected in female patients with a strong familial clustering of diabetes, with predominantly maternal transmission of disease and the presence of sensorineural deafness.
- Genetic analysis → A3243G mutation in the tRNA gene

Treatment

- with type 2 DM presentation: due to an underlying mitochondrial mutation can be with sulfonylureas is the initial treatment of choice
- Metformin is contraindicated due to risk of development of lactic acidosis.**
 - A mitochondrial dysfunction in muscle is expected to lead to a higher lactate
 - The A3243G mutation was originally detected in patients with mitochondrial myopathy, encephalopathy, **lactic acidosis**, and stroke-like episodes (MELAS syndrome)

Mitochondrial diseases follow a maternal inheritance pattern

- All children of affected females will inherit it.
- All children of affected males will not inherit the disease.

High glucose + sensorineural deafness → think of mitochondrial diabetes

Diabetes in pregnancy

Classification of diabetes in pregnancy

- Gestational diabetes (GDM) (developed during pregnancy): most common → 87.5% of all diabetic pregnancies.
- Pre-existing type 1 or type 2 diabetes

Epidemiology

- The prevalence of diabetes in pregnancy is 2–5% in the UK of both gestational diabetes and pre-existing diabetes.

Definition

- GDM refers to diagnosis of diabetes at 24 to 28 weeks of gestation.
- Diagnosis of diabetes in early pregnancy is more consistent with previously undiagnosed type 2 diabetes.

Gestational diabetes mellitus (GDM)

Risk factors for GDM

- BMI of $> 30 \text{ kg/m}^2$
- previous macrosomic baby weighing 4.5 kg or above
- previous gestational diabetes
- first-degree relative with diabetes
- family origin with a high prevalence of diabetes (South Asian, black Caribbean and Middle Eastern)

Screening for GDM

- Women who've previously had gestational diabetes:
 - ⇒ Oral glucose tolerance test (**OGTT**) should be performed as soon as possible after booking **and** at 24-28 weeks if the first test is normal.
 - ⇒ NICE also recommend that early self-monitoring of blood glucose is an alternative to the OGTTs.
- Women with any of the other risk factors → OGTT at 24-28 weeks

Diagnosis: GDM is diagnosed if either:

- Fasting glucose is $\geq 5.6 \text{ mmol/l}$
- 2-hour glucose is $\geq 7.8 \text{ mmol/l}$
- **If fasting blood glucose between 5.5 and 7.0 mmol/l then proceed to → 75-g oral glucose tolerance test**

The oral glucose tolerance test remains the investigation of choice for gestational diabetes

Complications

- Macrosomia (the commonest complications)
 - ⇒ defined by a birth weight $> 4.5\text{Kg}$
 - ⇒ affects up to 45% of babies
 - ⇒ **shoulder dystocia is a common delivery problem occurring in up to 15 – 20% of cases.**
- Neonatal hypoglycaemia
- Maternal complications are hypertension, preeclampsia, increased risk of developing diabetes mellitus and increased risk of cesarean delivery.

Management

- Advice about diet (including eating foods with a low glycaemic index) and exercise should be given
- Aspirin should also be considered given the increased risk of pre-eclampsia.
- **If the fasting plasma glucose level is $< 7 \text{ mmol/l}$**
 - ⇒ **Trial of diet and exercise should be offered**
 - ⇒ If glucose targets are not met within 1-2 weeks of altering diet/exercise metformin should be started
 - ⇒ If glucose targets are still not met insulin should be added to diet/exercise/metformin

- If at the time of diagnosis, the fasting glucose level is $\geq 7 \text{ mmol/l}$
⇒ insulin should be started
- If the plasma glucose level is between 6-6.9 mmol/l, and there is evidence of complications such as macrosomia or hydramnios:
⇒ insulin should be offered
- Fasting blood glucose should be checked 6 -13 weeks postpartum

Prognosis

- the incidence of type 2 diabetes in women with a history of gestational diabetes is 16%

Pre-existing diabetes in pregnancy

Complications

- the risk of severe congenital malformation increased by two-fold in infants born to mother with pre-existing diabetes (pregestational diabetes)

Management

- Planning pregnancy
 - ⇒ Patients should achieve good diabetic control prior to planning for pregnancy.
 - ⇒ If this has not been achieved, then NICE advises contraception and to offer termination if pregnancy does occur due to increased risks in pregnancy.
 - ⇒ Control will reduce the risk of miscarriage, congenital malformation, stillbirth, and neonatal death.
- Stop oral hypoglycaemic agents, apart from metformin, and commence insulin
- Folic acid 5 mg/day from pre-conception to 12 weeks gestation
- Aspirin 75mg/day from 12 weeks until the birth of the baby, to reduce the risk of pre-eclampsia
- Detailed anomaly scan at 20 weeks including four-chamber view of the heart and outflow tracts
- Tight glycaemic control reduces complication rates
- Treat retinopathy as can worsen during pregnancy
 - ⇒ It is advised, however, if the patient has not had retinal screening within the last six months to offer this urgently as there can be rapid development of diabetic retinopathy in pregnancy.
- Continuous glucose monitoring (CGM) improves glucose control

Patients with diabetes should have increased frequency of retinal screening during pregnancy due to increased risk of retinopathy

Targets for self-monitoring of pregnant women (pre-existing and gestational diabetes)

Time	Target
Fasting	5.3 mmol/l
1 hour after meals	7.8 mmol/l, or
2 hour after meals	6.4 mmol/l

Lipids and obesity problems

Obesity: overview

Classification

Classification	Body Mass Index (BMI) kg/m ²
Healthy weight	18.5-24.9
Overweight	25-29.9
Obesity I	30-34.9
Obesity II	35-39.9
Obesity III (Morbid obesity)	40 or more

Associated conditions

- Metabolic syndrome (hypertension, hyperglycaemia, hyperlipidaemia)
- GI conditions: cholelithiasis, nonalcoholic fatty liver disease, GERD, colonic diverticulosis
- Respiratory: Obstructive sleep apnea (OSA), obesity hypoventilation syndrome (Pickwickian syndrome)
- Polycystic ovary syndrome
- Mental health issues: e.g., depression , anxiety, eating disorders
- Gout

Hormonal alterations in obesity

- **Increased in obesity**
 - ⇒ **Testosterone (female):** due to insulin resistance (PCOS) ↓ SHBG
 - ⇒ **LH in (female):** due to insulin resistance
 - ⇒ **Insulin:** due to ↑ insulin resistance
 - ⇒ **Renin:** due to ↑ Sympathetic tone
 - ⇒ **Aldosterone:** due to ↑ Adipokines, renin- angiotensin, leptin
 - ⇒ **Leptin :** due to increased adipose mass, Leptin resistance
- **Decreased in obesity**
 - ⇒ **Testosterone (male):** due to ↓ SHBG ↑ aromatase ↓ GnRH
 - ⇒ **LH/FSH (male):** due to ↑ oestrogens/androgens
 - ⇒ **Glucagon-like peptide-1 (GLP-1):** due to ↑ FFA
 - ⇒ **25-OH vitamin D:** due to trapping in adipose tissue, ↓ sun exposure, ↓ 25OH vitamin D binding protein ↓ liver synthesis.
 - ⇒ **Ghrelin**

Obesity hormones

- Leptin Lowers appetite
- Ghrelin Gains appetite

Appetite regulation (ghrelin and leptin)

Leptin (the satiety hormone)	Ghrelin (the hunger hormone)
<ul style="list-style-type: none"> • Produced by adipose tissue. • Acts on ventromedial area of hypothalamus (satiety center) to ↓↓ appetite. • Obese people have ↑↑ leptin due to ↑↑ adipose tissue but are tolerant or resistant to leptin's anorexigenic effect. • Mutation of leptin gene → severe obesity. • Factors → ↓↓ leptin <ul style="list-style-type: none"> ⇒ Starvation ⇒ Sleep deprivation 	<ul style="list-style-type: none"> • Produced by stomach • Acts on hypothalamus to ↑↑ hunger, ↑↑gastric acid secretion and ↑↑GIT motility. Acts synergistically with GnRH to stimulate growth hormone release • Regulate appetite → stimulates hunger • Factors → ↑↑ghrelin <ul style="list-style-type: none"> ⇒ Empty stomach (fasting) ⇒ Sleep deprivation ⇒ Prader-Willi syndrome • Factors → ↓↓ghrelin <ul style="list-style-type: none"> ⇒ Stretched stomach

Ghrelin makes you grow hungry (the hunger hormone).

Leptin keeps you thin (the satiety hormone).

Obesity: management (step-wise approach)

Lifestyle modifications

- Reduce fat intake
 - ⇒ The current UK recommendations: total fat intake should be restricted to less than 30% of dietary energy (the average daily energy consumption of a male is 2500 kcal and 2000 kcal for a female.)
- Physical activity: at least 30 minutes of moderate aerobic activity 5–7 times per week.

Pharmacological management: Anti-obesity drugs

- **Indications:**
 - ⇒ body mass index (BMI) ≥ 30 kg/m² in whom at least three months of managed care involving supervised diet, exercise and behaviour modification fails.
 - ⇒ **BMI ≥ 28 kg/m² + risk factors** (eg: diabetes mellitus, coronary heart disease, hypertension and obstructive sleep apnoea)
- **Discontinuation:** Anti-obesity drug treatment should be discontinued :
 - ⇒ If weight loss is less than 5% after the first 12 weeks.
 - ⇒ **If the individual regains weight at any time whilst receiving drug treatment**
- **Contraindications:**
 - ⇒ Combination drug therapy is contraindicated

- ⇒ Drugs should never be used as the sole element of treatment (should only be prescribed as part of an overall plan for managing obesity).

- **Orlistat**

- ⇒ **Action** : **pancreatic lipase inhibitor**, blocks the breakdown and hence the absorption of dietary fat.
- ⇒ Normally used for < 1 year
- ⇒ **Adverse effects**: faecal urgency/incontinence and flatulence.

Surgical management: bariatric surgery

Obesity - NICE bariatric referral cut-offs

- with risk factors (T2DM, BP etc): $> 35 \text{ kg/m}^2$
- no risk factors: $> 40 \text{ kg/m}^2$

- **Benefits**

- ⇒ **Reduces cardiovascular mortality** (the risks of long-term obesity outweigh those of surgery.)

- **Indications as third line option** after failure of lifestyle modifications and anti-obesity drugs **to achieve or maintain adequate weight loss for at least 6 months + the patient is fit for surgery + commit to the need for long-term follow-up:**

- ⇒ $\text{BMI} \geq 40 \text{ kg/m}^2$
- ⇒ $\text{BMI} \geq 35 \text{ kg/m}^2$ and other significant disease (eg: type 2 DM, hypertension, sleep apnea)

- **Indications as first-line option**

- ⇒ $\text{BMI} > 50 \text{ kg/m}^2$ (consider orlistat before surgery if the waiting time is long)

- **Which procedures?**

- ⇒ **Laparoscopic-adjustable gastric banding (LAGB)** is the **first-line intervention in patients with a BMI of 30-39kg/m²** (produces less weight loss than malabsorptive or mixed procedures but as it has fewer complications)
- ⇒ **Sleeve gastrectomy** (most common form of bariatric surgery) may be considered for patients with a **BMI > 40 kg/m²**
- ⇒ **Primarily malabsorptive** procedures (e.g. biliopancreatic diversion with duodenal switch) are usually reserved for **very obese patients (e.g. BMI > 60 kg/m²)**

Lipid disorders: Overview

Causes

- **Acquired (more common)**

- ⇒ Obesity
- ⇒ Diabetes mellitus
- ⇒ Heavy consumption of alcohol
- ⇒ Hypothyroidism
- ⇒ Nephrotic syndrome
- ⇒ Cholestatic liver disease
- ⇒ Cushing disease
- ⇒ Drugs: antipsychotics, beta blockers (e.g., metoprolol), oral contraceptive pill, high-dose diuretic use

- **Inherited (less common)**

Pathophysiology

- Elevated LDL and reduced HDL → promote atherosclerosis → increased risk of cardiovascular events

Classification: WHO/Fredrickson classification

Classification	Aetiology	Lipid profile	Notes
Type 1 Familial Hyper-Chylomicronaemia	Deficiency of Apo CII or LPL (lipoprotein lipase)	↑ chylomicrons	typically presents with eruptive xanthoma, abdominal colic, acute pancreatitis
Type 11A Familial hypercholesterolaemia	LDL-receptor deficiency	↑TC > 7.5 ↑LDL-C > 4.9	Heterozygous type is Common Associated with tendon xanthoma
Type 11B Familial Combined Hyperlipidaemia	overproduction of apo B-100 &(VLDL) by the liver	↑ LDL ↑VLDL ↑TG	The commonest type (two thirds). Associated with glucose intolerance.
Type 111 Remnant hyperlipidaemia (dysbetalipoproteinaemia)	Abnormal ApoE	↑ IDL	palmar xanthoma is diagnostic fibrates are first line treatment
Type 1V Familial hypertriglyceridaemia	Overproduction or↓ catabolism of VLDL (due to ↓ LPL)	↑TG ↑VLDL	often "polygenic". Common

abdominal pain, eruptive xanthoma and strong family history = think of Chylomicronaemia

Lipoproteins

• High density lipoprotein (HDL)

- ⇒ Secreted by intestinal epithelium and liver
- ⇒ **Composition:** Mostly proteins and phospholipids
- ⇒ **Function:** Transport cholesterol from peripheral tissues (e.g., atherosclerotic arteries) to the liver (reverse cholesterol transport), where it is excreted (e.g., via bile)
- ⇒ Often referred to as "**good cholesterol**."
- ⇒ Low levels of HDL are associated with an increased risk of ischaemic heart disease
- ⇒ Among other apoproteins, HDL contains **Apo A-1, which is found only in HDL.**
- ⇒ **Causes of ↑HDL**
 - Exercise
 - modest alcohol consumption.
 - ↑oestrogen levels (e.g. contraceptive pill). Women have naturally higher HDL levels compared to men, due to higher oestrogen levels.
- ⇒ **Causes of ↓HDL**
 - Diabetes causes low HDL

• Low-density lipoprotein (LDL)

- ⇒ Arise from IDL that is modified by hepatic lipases in peripheral tissue and the liver
- ⇒ **Composition:** Mostly cholesterol
- ⇒ **Function:** Transport cholesterol from the liver to peripheral tissues and arteries

- ⇒ Often referred to as "**bad cholesterol**"
- ⇒ they carry only one apolipoprotein, **Apo B-100** which binds tissue LDL receptors to facilitate receptor-mediated uptake of cholesterol.

- **Intermediate-density lipoprotein (IDL)**

- ⇒ Formed from VLDL degradation
- ⇒ **Function** : Transport triglycerides and cholesterol to the liver

- **Very low-density lipoprotein (VLDL)**

- ⇒ **Secreted by** the liver
- ⇒ **Composition:** Mostly triglycerides
- ⇒ **Function:** Transport hepatic triglycerides from the liver to peripheral tissues

- **Chylomicron**

- ⇒ **Composition:** Mostly triglycerides
- ⇒ **Secreted by** the intestinal epithelial cells into lymphatics
- ⇒ The nascent (early) chylomicron contains only one apoprotein, **Apo B-48**.
- ⇒ **Function:**
 - Transport dietary triglycerides from the intestine to peripheral tissues
 - Transport dietary cholesterol to the liver in the form of triglyceride-depleted chylomicron remnants
- ⇒ Lipoprotein lipase (**LPL**) hydrolyses the chylomicron into glycerol, fatty acids, and chylomicron remnant using Apo C-2 as a co-factor. **Deficiencies of LPL or Apo C-2 cause familial hyperchylomicronemia.**
- ⇒ Apo **E** mediates **Endocytosis of chylomicron remnants**

Apolipoproteins

- The following table shows the apolipoproteins present on the surface of various lipoproteins:

Lipoproteins	apolipoproteins
Chylomicron	Apo CII & Apo B48
Chylomicron remnant	Apo E
VLDL	Apo CII & Apo B100
LDL	Apo B100
IDL	Apo E & Apo B100
HDL	Apo A1

Familial Combined Hyperlipidaemia (type IIB)

Overview

- Type IIB in Frederickson classification of inherited hyperlipoproteinemia
- **Commonest type** (two thirds)
- Prevalence → 1%
- Autosomal dominant
- polygenic disorder
- Pathogenesis: Defective LDL receptors or **ApoB-100**
- Hepatic overproduction of apoB-100-containing lipoprotein particles (ie, VLDL and LDL), →↑total cholesterol, triglycerides, and apoB levels

- Associated with: Obesity, glucose intolerance, and hyperuricaemia

Features

- Xanthelasma
- premature cardiovascular disease**
- ↑ LDL, ↑ VLDL, ↑ TG

Treatment

- Statins (e.g. atorvastatin)

Which feature suggests a diagnosis of familial combined hyperlipidaemia (FCHL) rather than heterozygous familial hypercholesterolaemia (FH)?

- Presence of glucose intolerance

Remnant hyperlipidaemia (type III)

Overview

- Type III in Frederickson classification of inherited hyperlipoproteinemia
- Autosomal recessive
- Pathogenesis: Defective ApoE → accumulation of IDL and chylomicron remnants

Features

- Premature atherosclerosis
- Palmar and tuberoeruptive xanthomas
- ↑ Total cholesterol, ↑ triglycerides, ↑ Chylomicrons, ↑ VLDL

Diagnosis

- Definitive diagnosis can be made by lipoprotein electrophoresis or genotyping of apoprotein E.

Management

- fibrates are first line treatment
 - ⇒ mode of action → Increased lipoprotein lipase activity via PPAR-alpha (PPAR-alpha agonist)

Palmar xanthomas are pathognomonic of dysbetalipoproteinaemia (type III hyperlipoproteinemia).

Familial hypertriglyceridaemia

Overview

- Type IV in Frederickson classification of inherited hyperlipoproteinemia
- Autosomal dominant condition
- Usually due to polygenic factors
- Affects 1 in 300 people.**
- Can be exacerbated by:
 - ⇒ alcohol
 - ⇒ glucocorticoids
 - ⇒ thiazide diuretics

Pathogenesis

- **Hepatic over production of VLDL**

- ↓ lipoprotein lipase (a potent metabolizer of triglycerides within VLDL) → accumulation of VLDL molecules and triglycerides.

Features

- Premature atherosclerosis
- Acute pancreatitis if triglyceride levels are very high ($>11 \text{ mmol/l}$), likely due to pancreatic capillary obstruction.
- Features of hyperglycemia (due to abnormal glucose tolerance and insulin resistance)
- **Eruptive xanthomas** (yellow papules usually seen on the back, chest, and proximal extremities).
- **Lipemia retinallis** (pale pink milky appearance to the retinal vessels or even to the retina itself).
- Retinal vein thrombosis

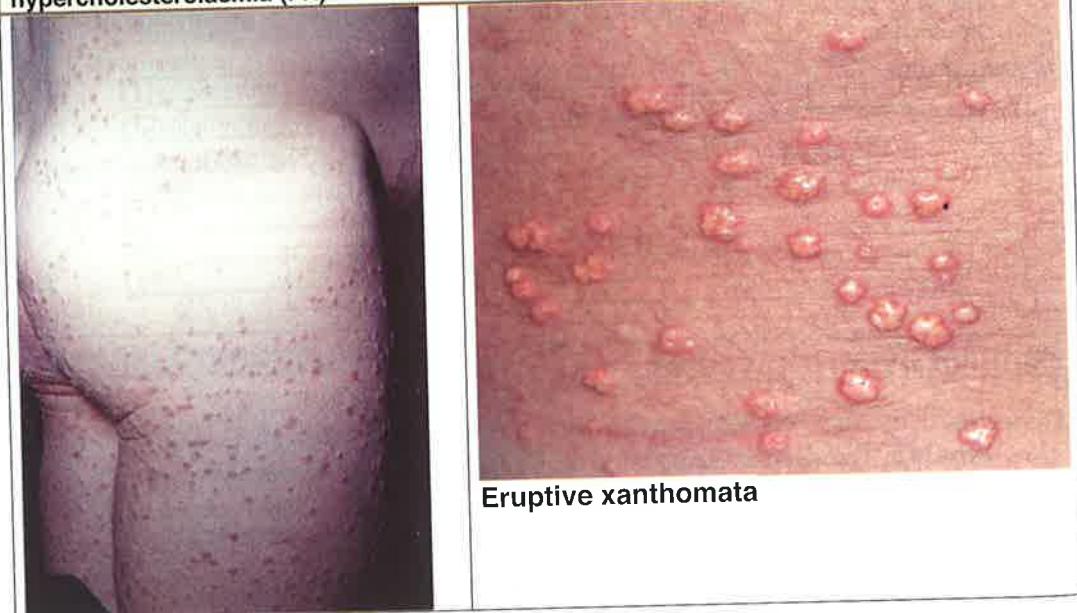
Diagnosis

- **Lipid profile**
 - ⇒ raised very-low-density lipoprotein (VLDL) and triglyceride levels.
 - ⇒ total cholesterol and LDL levels are typically normal

Management

- first-line → fibrates
- statins if there is mixed hyperlipidaemia

Tendon xanthomata are diagnostic hallmarks of heterozygous familial hypercholesterolaemia (FH)



Familial hypercholesterolaemia (FH)

Overview

- Type II in Frederickson classification of inherited hyperlipoproteinemia
- Autosomal dominant condition
- Caused by mutations in the gene which encodes the LDL-receptor protein.
- Heterozygous FH occur in about 1 in 300. Homozygous patients are rare
- Affect around 1 in 500 people.

1111

Pathogenesis

- Defective LDL receptors or ApoB-100, missing LDL receptors

Features

- early cardiovascular disease (CVD)
- Tuberous/tendon xanthomas (especially the Achilles tendon)
- Xanthelasma
- High levels of LDL-cholesterol which, if untreated, may cause

Suspected diagnosis: NICE advice to suspect diagnosis of FH if:

- total cholesterol level **>7.5 mmol/l**
- premature coronary heart disease (<60 years) in an index individual or first-degree relative.
- children of affected parents:
 - ⇒ if one parent is affected, arrange testing in children by age 10
 - ⇒ if both parents are affected, arrange testing in children by age 5

Clinical diagnosis is now based on the **Simon Broome criteria**:

- Total cholesterol (TC) **> 7.5 mmol/l and LDL-C > 4.9 mmol/l plus:**
 - ⇒ **For definite FH:** tendon xanthoma in patients or 1st or 2nd degree relatives or DNA-based evidence of FH
 - ⇒ **For possible FH:** family history of myocardial infarction below age 50 years in 2nd degree relative, below age 60 in 1st degree relative, or a family history of raised cholesterol levels
- If LDL-C **>13 mmol/l** → Consider a clinical diagnosis of **homozygous FH**
- **Two measurements of LDL-C** are required to confirm the diagnosis.

The presence of tendon xanthomata and ↑LDL, ↑T.chol → familial hypercholesterolemia.

Management

- **First-line:** high-dose statins
 - ⇒ statins should be discontinued in women 3 months before conception due to the risk of congenital defects
 - ⇒ aim for at least a 50% reduction in LDL C concentration from the baseline measurement
- **Second-line** (if statin therapy is not tolerated or contraindicated) or if lipid not controlled by statin alone → Ezetimibe
- **Third-line:** (If statins or ezetimibe are not tolerated or contraindicated) → either a bile acid sequestrant (resin) or a fibrate
- **Fourth-line: LDL apheresis:** for homozygous or heterozygous FH who did not respond to drugs

- ⇒ ACE inhibitors should not be used in people who are being treated with LDL apheresis. Instead, angiotensin-receptor blocking agents should be used.
- ⇒ warfarin should be discontinued 4 days before LDL apheresis and substituted with low molecular weight heparin.
- Fifth-line: Liver transplantation
- Screening for first-degree relatives (they have a 50% chance of having the disorder). This includes children who should be screened by the age of 10 years if there is one affected parent.
- Lifestyle interventions: Diet
 - ⇒ total fat intake is 30% or less of total energy intake
 - ⇒ saturated fats are 10% or less of total energy intake
 - ⇒ intake of dietary cholesterol is less than 300 mg/day

Lipid-lowering therapy in patients with ACS: (2019 ESC/EAS Guidelines for the management of dyslipidaemias)

- For patients who present with an ACS, and whose LDL-C levels are not at goal despite already taking a maximally tolerated statin dose and ezetimibe, adding a PCSK9 inhibitor early after the event (if possible, during hospitalization for the ACS event) should be considered.

Secondary hypertriglyceridaemia

The commonest cause of a mild hypertriglyceridaemia is obesity secondary to a reduced efficacy of lipoprotein lipase activity and overproduction of VLDL.

Causes of predominantly hypertriglyceridaemia

- Obesity
 - ⇒ The commonest cause of a mild hypertriglyceridaemia is obesity secondary to a reduced efficacy of lipoprotein lipase activity and overproduction of VLDL.
 - ⇒ hypertriglyceridaemia and raised transaminases are suggestive of increased hepatic fat → associated with Non-alcoholic steatohepatitis (NASH)
- Type 2 diabetes mellitus
 - ⇒ Bad diabetic control ($\uparrow\uparrow$ HbA_{1c}) → ↓ activity of lipoprotein lipase (LPL) (because LPL requires insulin for full activity) → hypertriglyceridaemia and low high-density lipoprotein (HDL)
- Alcohol
- Chronic renal failure
- Drugs: thiazides, non-selective beta-blockers, unopposed oestrogen
- Liver disease

Causes of predominantly hypercholesterolaemia

- Nephrotic syndrome
- Cholestasis
- Hypothyroidism
 - ⇒ Frank hypothyroidism is said to occur in 4% of patients with dyslipidaemias;
 - ⇒ a raised thyroid-stimulating hormone (TSH) & normal free T4 occur in 10% of patients with dyslipidaemia
 - ⇒ Total cholesterol often improves to some degree with thyroxine therapy but statins might be required as well.

High triglycerides and low high-density lipoprotein (HDL) cholesterol are the commonest lipid abnormality seen in type 2 diabetes.

Hypercholesterolaemia rather than hypertriglyceridaemia: nephrotic syndrome, cholestasis, hypothyroidism

Complications

- Increased risk of CVD events
- **Increased insulin resistance**

Management

- With DM → the first priority in this patient is to improve the glucose control.
- JBS2 guidelines suggest that all patients with type 2 diabetes should be prescribed a **statin**, even if their cholesterol is within the target range.
- If triglyceride level > 20 mmol/L that is not a result of excess alcohol or poor glycaemic control, refer for urgent specialist review (i.e. at a regional lipid clinic).
- If triglyceride level between 10 and 20 mmol/L:
 - ⇒ Repeat the triglyceride with a fasting test (following a meal, the chylomicron level rises in the serum which will lead to a rise in triglyceride levels)
 - ⇒ Look for secondary causes
 - ⇒ Address **lifestyle** factors: encourage weight loss, healthy diet and exercise
 - ⇒ Commence high-potency **statins** (atorvastatin, rosuvastatin) if unable to address the triglyceride level through lifestyle measures.

Fibrates (e.g. fenofibrate).

- The best initial medical treatment for hypertriglyceridemia.
- Action: **PPAR alpha receptor agonists** → **increasing the activity of lipoprotein lipase**
- Does not reduce cardiovascular events in the presence of diabetes, while statins have. Thus, **an isolated hypertriglyceridaemia in the presence of significant cardiovascular risk factors, in a patient not currently on a statin, should be managed with the introduction of a statin.**
- Concomitant fibrate-statin use is associated with an increased risk of myopathy.

Omega-3

- Trials of omega 3 supplementation suggest that it is associated with triglyceride reduction of up to 38%.
- **OMACOR (omega-3-acid ethyl esters) : Mode of action** → Increases peroxisomal beta-oxidation of fatty acids in the liver
- 2019 ESC/EAS Guidelines for the management of dyslipidaemias: (In high-risk patients with TG between 1.5 and 5.6 mmol/L (135 - 499 mg/dL) despite statin treatment, n-3 PUFAs (icosapent ethyl 2 g/day) should be considered in combination with statins
- Icosapent ethyl is an ethyl ester of the omega-3 fatty acid eicosapentaenoic acid (EPA).

Nicotinic acid

- It lower both cholesterol and triglyceride concentrations by inhibiting synthesis and increases HDL-cholesterol when used in doses of 1.5-3g daily.
- It is recommended for use by specialists in combination with a statin, where a statin alone

- Add of nicotinic acid → raise HDL cholesterol level by great amount
- the value of nicotinic acid is limited by its side-effects (especially vasodilatation)
- may increase blood glucose in some patients. many mechanisms have been suggested for this:
 - ⇒ Since **nicotinic acid inhibits triglyceride synthesis**, it may be that the increased availability of free fatty acids stimulates hepatic glucose output by increasing gluconeogenesis or replacing glucose as the primary energy source.
 - ⇒ Higher levels of fatty acids may also block glucose uptake by skeletal muscle.
 - ⇒ Direct effects on beta-cell function have also been postulated.
- For people with a triglyceride concentration **between 4.5 and 9.9 mmol/L**, optimize the management of other CVD risk factors present.

Which lipid abnormalities are most likely to be detected in a patient with type 2 diabetes?

- **Small dense LDL molecules** (LDL is not typically elevated in type 2 diabetes)
- ↓↓ HDL
- ↑↑Triglycerides

Question

Analysis of a patient lipoprotein profile shows a deficiency of apolipoprotein C-II. All other lipoproteins are normal.

Which lipid profile is most likely to be shown?

Answer → **Elevated levels of both chylomicrons and VLDLs**

- Apolipoprotein C-II (Apo C-II) is an essential co-factor of lipoprotein lipase, which hydrolyzes triglyceride in chylomicrons and VLDLs.

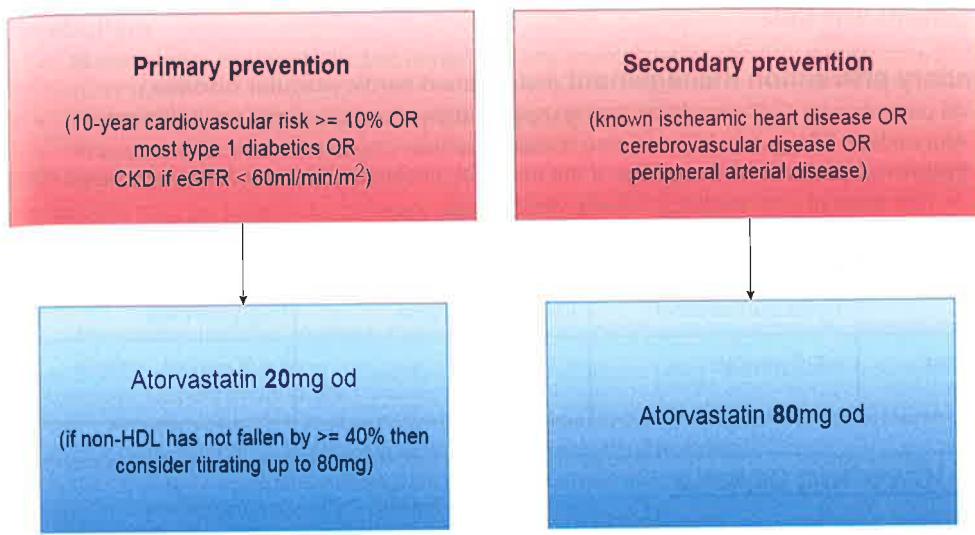
Xanthomas

- **Tuboeruptive xanthomas** occur in type III hyperlipoproteinaemia
- **Eruptive xanthomas** are associated with hyperchylomicronaemia (type I and type V hyperlipoproteinaemia)
- **Xanthoma tendinosum**, which are nodular swellings of tendons, usually occur in type II hyperlipoproteinaemia

Hyperlipidaemia: management

In the primary prevention of CVD using statin aim for a reduction in non-HDL cholesterol of $\geq 40\%$

Graphic showing choice of statin.



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Statins reduce all-cause mortality (not just cardiovascular mortality) in primary prevention

Primary prevention - risk assessment

- NICE recommend use the **QRISK2** CVD risk assessment tool for patients aged ≤ 84 years.
- High risk of cardiovascular disease (CVD), defined as a 10-year risk of **10%** or greater.
- **QRISK2 should not be used in the following situations:**
 - ⇒ Patients ≥ 85 years are already at high risk of CVD due to their age
 - ⇒ type 1 diabetics
 - ⇒ patients with an estimated glomerular filtration rate (eGFR) less than 60 ml/min and/or albuminuria.
 - ⇒ patients with a history of familial hyperlipidaemia.
- **NICE suggest QRISK2 may underestimate CVD risk in the following:**
 - ⇒ people treated for HIV
 - ⇒ Serious mental health problems
 - ⇒ people taking medicines that can cause dyslipidaemia such as antipsychotics, corticosteroids or immunosuppressant drugs
 - ⇒ Autoimmune disorders/systemic inflammatory disorders such as systemic lupus erythematosus.
- **Measuring lipid levels**
 - ⇒ The samples does not need to be fasting.
 - ⇒ repeat sample (fasting or non-fasting) before deciding on further management

Primary prevention management (No established cardiovascular disease)

- If the QRISK2 10-year risk is $\geq 10\%$ → Atorvastatin 20mg should be offered first-line + Lifestyle changes
- People with Type 1 diabetes mellitus:** atorvastatin 20 mg should be offered if type 1 diabetics who are: age > 40 years, or diabetes for more than 10 years or nephropathy or CVD risk factors.
- People with type 2 diabetes** → If the QRISK2 10-year risk is $\geq 10\%$ → atorvastatin 20 mg
- People with Chronic kidney disease (CKD):** atorvastatin 20mg should be offered to all patients with CKD

Secondary prevention management (established cardiovascular disease)

- All patients with CVD should be taking a statin in the absence of any contraindication.
- Atorvastatin **80mg** should be offered first-line.
- Follow-up patients at 3 months:** if the non-HDL cholesterol has not fallen by at least 40% → ↑the dose of atorvastatin gradually up to 80mg.

Targets of management

	Total cholesterol	LDL cholesterol	Triglycerides
Joint British Societies	< 4.0 mmol/l	< 2.0 mmol/l	< 1.7 mmol/L

Lipid-lowering agents**Mechanism of action and adverse effects**

The following table compares the side-effects of drugs used in hyperlipidaemia:

Drugs	Mechanism of action	Adverse effects
Statins	HMG CoA reductase inhibitors	Myositis, deranged LFTs
Ezetimibe	Decreases cholesterol absorption in the small intestine	Headache
Nicotinic acid	Decreases hepatic VLDL secretion	Flushing, myositis
Fibrates	Agonist of PPAR-alpha therefore increases lipoprotein lipase expression	Myositis, pruritus, cholestasis
Cholestyramine	Decreases bile acid reabsorption in the small intestine, upregulating the amount of cholesterol that is converted to bile acid	GI side-effects

PPAR- α agonists (The fibrate) → ↓serum triglyceride levels and ↑HDL-cholesterol

PPAR- γ agonists (the glitazones) → ↓free fatty acid levels → ↓insulin resistance → ↓blood glucose levels

Statins

Statins inhibit HMG-CoA reductase, the rate-limiting enzyme in hepatic cholesterol synthesis

Action

- Statins inhibit the action of HMG-CoA reductase, the rate-limiting enzyme in hepatic cholesterol synthesis

Metabolism

- Simvastatin, atorvastatin and lovastatin are mainly metabolized by cytochrome P450 (CYP) 3A4.
- Fluvastatin and rosuvastatin is metabolized by CYP2C9
- Pravastatin is excreted largely unchanged.

Pravastatin may be suitable for primary prevention, but in high-risk secondary prevention patient, a stronger agent is required such as rosuvastatin.

Adverse effects

- **Myopathy:** includes myalgia, myositis, rhabdomyolysis and asymptomatic raised creatine kinase.
 - ⇒ Occurs in up to 5%.
 - ⇒ More common in lipophilic statins (simvastatin, atorvastatin) than relatively hydrophilic statins (**rosuvastatin, pravastatin, fluvastatin**)
 - ⇒ If only myalgia (muscle pain): continue treatment as long as creatinine phosphokinase (CK) remain normal.
 - ⇒ Before offering a statin, if CK levels are **5 times the upper limit of normal** (repeated 2 times), do not start statin treatment. If CK levels are raised but less than 5 times the upper limit of normal, **start statin treatment at a lower dose**.
 - ⇒ Starting at a low dose and gradually titrating up can also minimise the risk of side effects: for example, start at 5 mg of rosuvastatin.
- **Hepatotoxicity:**
 - ⇒ Occurs in ~ 2% of patients
 - ⇒ ↑ LFTs due to the involvement of cytochrome P450 systems (CYP3A4 and CYP2C9) in the breakdown of statins
 - ⇒ Check LFTs at baseline, 3 months and 12 months, but not again unless clinically indicated.
 - ⇒ Statins should be discontinued if serum transaminase concentrations rise to and persist at **3 times the upper limit** of the reference range. **If LFT are raised but less than 3 times the upper limit of normal:**
 - 1st step: **NICE advises reducing the dose in the first instance.**
 - 2nd step: Consider an alternative statin.
- **Statins may increase the risk of intracerebral haemorrhage in patients who've previously had a stroke.** For this reason the Royal College of Physicians recommend avoiding statins in patients with a history of intracerebral haemorrhage.
 - ⇒ This effect is not seen in primary prevention.

Maintain a high index of suspicion for rhabdomyolysis if muscle pain occurs after administering statins

Drug interactions with statins

P450 inhibitors ↑ CK and myopathy

- P450 inhibitors (e.g. HIV protease inhibitors, Macrolides (especially erythromycin and clarithromycin), Azole antifungals, **Cyclosporine, grapefruit juice**) → ↑ serum statins → precipitate Myopathy or rhabdomyolysis
- Other lipid-lowering agents (e.g. Fibrates and Nicotinic acid)
- Agents which can precipitate Myopathy or rhabdomyolysis
 - ⇒ **calcium channel blockers**

Which statin is associated with the lowest risk of rhabdomyolysis?

→ Fluvastatin

Lipid lowering drugs and pregnancy

- Normally in pregnancy, cholesterol can increase by up to 50%
- Omega-3 fatty acids can be used safely in pregnancy as monotherapy, and function to decrease maternal TG levels.
- With the exception of the bile acid sequestrants (BAS) such as cholestyramine , cholesterol-lowering medications should be stopped prior to pregnancy
- NICE guidelines recommend stopping cholesterol-lowering medications 3 months before attempting to conceive.

Contraindications

1. Active liver disease
2. Muscle disorder
3. Pregnancy, breastfeeding: stop taking statins 3 months before attempt to conceive and do not restart until breastfeeding is finished.

Fibrates

Agents

- bezafibrate, fenofibrate, and gemfibrozil

Mechanism of action

- Activation of the peroxisome proliferator-activated receptor alpha (**PPAR-α**) → ↓ LDL, ↑ HDL, ↓↓ triglyceride
- Enhance lipoprotein lipase activity

Indication

- second-line drug of choice in hyperlipidemia, most effective for lowering triglycerides

Contraindications

- Renal insufficiency
- Liver failure
- Gall bladder diseases

Side effects

- Dyspepsia
- Myopathy
- **Cholelithiasis** (Cholesterol gallstones)
- ↑ LFTs (hepatotoxicity)

Interactions

- enhance the effect of other drugs by inhibiting hepatic CYP450 (e.g., sulfonylureas, warfarin)

Ezetimibe

Ezetimibe → reduces the absorption of cholesterol through the gut.

Mechanism of action

- Blocks cholesterol reabsorption at small intestine brush border via inhibiting NPC1L1 in the gut lumen → ↓ LDL

Indication

- Monotherapy: in contraindications or statin intolerance
- Combination therapy (statin and ezetimibe): in insufficient LDL cholesterol reduction by statins

Side effects (especially in combination therapy, otherwise rare):

- ↑ liver enzymes,
- angioedema,
- diarrhea,
- myalgia

Contraindication

- coadministration with a statin during active liver disease

Nicotinic acid (niacin)

Nicotinic acid increases HDL levels

Mechanism of action

- Inhibits lipolysis and fatty acid release in adipose tissue → ↓ triglyceride and LDL synthesis, ↑ HDL
- Niacin lowers LDL-C and increases HDL-C by:
 - ↓ hepatic VLDL synthesis and secretion into circulation,
 - ↓ lipolysis in peripheral adipose tissue.

Indication

- high LDL cholesterol and lipoprotein(a) levels (> 50 mg/dL) despite statin and ezetimibe therapy (or if statins are contraindicated)
- Nicotinic acid is highly effective at raising high density lipoprotein (HDL) cholesterol**

Adverse effects

- Flushing:** NSAIDs (e.g., aspirin, ibuprofen) taken 30–60 minutes before niacin can prevent flushing by inhibiting prostaglandin synthesis.
- Hyperglycemia** (impaired glucose tolerance) → ↑ HbA1c in diabetics
- Irritates the gastric mucosa, exacerbates gastroesophageal reflux. **contraindicated in patients with active peptic ulcer disease**
- Myositis
- Hyperuricemia** → precipitates acute gout
- ↑ LFTs

Contraindications

- Liver failure
- Gout
- Hemorrhage
- Gastric ulcer
- Cardiovascular instability

Cholestyramine

Mechanism of action

- bile acid sequestrant
- bind bile acids in the intestine to prevent reabsorption and recycling
 - ⇒ forces liver to consume cholesterol in the process of making more bile salts
 - ⇒ binds bile acids in the intestine → interruption of enterohepatic circulation (\downarrow bile acid absorption and \uparrow bile acid excretion) → lowers cholesterol
- The main effect on lipid profile → reduce LDL cholesterol (\downarrow unbound LDL),
 - ⇒ causes \uparrow in LDL-receptor synthesis

Indications

- management of hyperlipidaemia.
 - ⇒ Combination treatment with statins in hypercholesterolemia
- Digitalis overdose
- Pruritus associated with elevated bile acid levels (cholestasis)
- Bile acid diarrhea
- Bowel obstruction
- occasionally used in Crohn's disease for treatment resistant diarrhoea.

Adverse effects

- abdominal cramps and constipation
- **decreases absorption of fat-soluble vitamins (e.g: vitamin D absorption will be reduced)**
 - ⇒ consider fat-soluble vitamin (vitamins A, D and K) and folic acid supplementation
- cholesterol gallstones
- \uparrow LFTs
- Myalgia
- may raise level of triglycerides

Contraindications

- **Hypertriglyceridemia** $>$ 300–500 mg/dL
- Hypertriglyceridemia-induced pancreatitis

Tangier disease

Overview

- rare autosomal recessive metabolic disorder.
- also known as **familial alpha-lipoprotein deficiency** or **hypoalphalipoproteinemia**

Features

- **Decreased levels or even a complete absence of high-density lipoproteins (HDL)**
- Low cholesterol levels
- cholesterol ester depositions especially in:
 - ⇒ Tonsils → **enlarged, yellow-orange tonsils**.
 - ⇒ Liver and spleen resulting in **hepatosplenomegaly**.

Abetalipoproteinemia

Treatment of abetalipoproteinemia involves dietary restriction of fats, and high-dose vitamin E therapy

Pathophysiology

- Rare **autosomal recessive** disorder
- Mutation in the microsomal triglyceride transfer protein → **deficiency of apolipoprotein B-48 and B-100** (both necessary for chylomicron formation and fat absorption) → deficiency of LDL, VLDL and chylomicrons.

Features

Typically presents in early childhood with steatorrhea, abdominal distension, and failure to thrive. During childhood or adolescence, progressive ataxia, neuropathy, and vision impairment develop.

- **Neurologic:** caused by **deficiency of vitamin E**
 - ⇒ cognitive decline
 - ⇒ **Clumsiness may be the first neurologic manifestation**
- Low visual acuity, caused by:
 - ⇒ Retinitis pigmentosa → do **fundoscopy**
 - ⇒ Vitamin A deficiency

Treatment

- **high-dose vitamin E**
- other fat-soluble vitamins (A, K, and D) should also be supplemented
- **restriction of long-chain fatty acids**

Disease associations with low LDL-C include malignancy and malabsorption

Causes of hypcholesterolaemia

- **Acquired:**
 - ⇒ Malignancy
 - ⇒ Malabsorption (Short-bowel syndrome, blind loop syndrome, celiac disease, pancreatic exocrine insufficiency, giardiasis)
 - ⇒ Anaemia (Thalassemia, pernicious anaemia)
 - ⇒ Chronic infection and infestations
 - ⇒ Severe illness in hospitalised patients
- **Genetic:**
 - ⇒ Hypobetalipoproteinemia (**most common genetic cause**),
 - ⇒ Abetalipoproteinemia

Gynaecomastia

Definition

- Gynaecomastia describes an abnormal amount of breast tissue in males and is usually caused by an **increased oestrogen: androgen ratio**.

Causes

- It is important to differentiate the causes of galactorrhoea (due to the actions of prolactin on breast tissue) from those of gynaecomastia

Causes of gynaecomastia

- physiological: normal in puberty
- syndromes with androgen deficiency:
Kallman's, **Klinefelter's (47, XXY karyotype)**
- testicular failure: e.g. mumps
- liver disease
- testicular cancer e.g. **seminoma** secreting hCG
- ectopic tumour secretion
- hyperthyroidism**
- haemodialysis
- starvation/refeeding
- drugs: see below

Drug causes of gynaecomastia (10-25% of cases)

Relatively Common causes

- spironolactone (most common drug cause)**
- cimetidine
- digoxin**
- cannabis
- diamorphine
- ciproterone
- finasteride
- gonadorelin analogues e.g. Goserelin, buserelin
- oestrogens, anabolic steroids

Very rare drug causes of gynaecomastia

- tricyclics
- isoniazid
- calcium channel blockers
- heroin
- busulfan
- methyldopa

September 2010 exam: H/O developed excessive amounts of breast tissue bilaterally.

Which one of the following drugs is most likely to be responsible? **Goserelin (Zoladex)**

Physiological changes during pregnancy – endocrine

pregnancy → ↑ oestradiol & prolactin + ↓ LH/FSH.

Progesterone

- Responsible for pregnancy maintenance
- Produced by the corpus luteum until the 10–12 weeks of gestation, after which it is produced by the fetoplacental unit

Human placental lactogen: a hormone synthesized by syncytiotrophoblasts of the placenta, which promotes the production of insulin-like growth factors.

- Increases insulin levels
- Causes insulin resistance

- Increases serum glucose levels and lipolysis to ensure sufficient glucose supply for the fetus
- Maternal insulin resistance begins in the second trimester and peaks in the third trimester.

Pituitary gland

- Hyperplasia of lactotroph cells in the anterior pituitary → physiological enlargement of the pituitary gland (up to 40% increase from pregestational volume)

Thyroid gland

- Thyroid gland hypertrophy**
 - The thyroid gland needs to produce 50% more thyroid hormone during pregnancy to maintain an euthyroid state.
 - A 10–20% increase in thyroid mass occurs.
- Increase in thyroid-binding globulin and albumin due to increased hepatic synthesis.**
 - Pregnancy** → ↑↑ thyroxine-binding globulin (TBG) → ↑↑ total thyroxine but does not affect the free thyroxine level
- Increase in total T3 and T4**
 - in normal pregnancy (T_3) and T_4 levels show a slight increase with suppressed (TSH) in the first trimester due to the partial thyroid-stimulating action of **human chorionic gonadotrophin (beta-HCG)**.
 - Free** T_3 and T_4 remains within normal ranges
- β -hCG-mediated hyperthyroidism (\downarrow TSH)**
 - β -hCG molecule has a similar structure to that of the TSH molecule. β -hCG binds to TSH receptors of the thyroid gland → thyroid stimulation → hyperthyroidism
- Factors influence thyroid function tests in the pregnant patient.**
 - thyroid stimulatory effects of hCG.**
 - HCG → activation of the TSH receptor → **transient gestational hyperthyroidism**.
 - HCG levels will fall in second and third trimester

Lipids

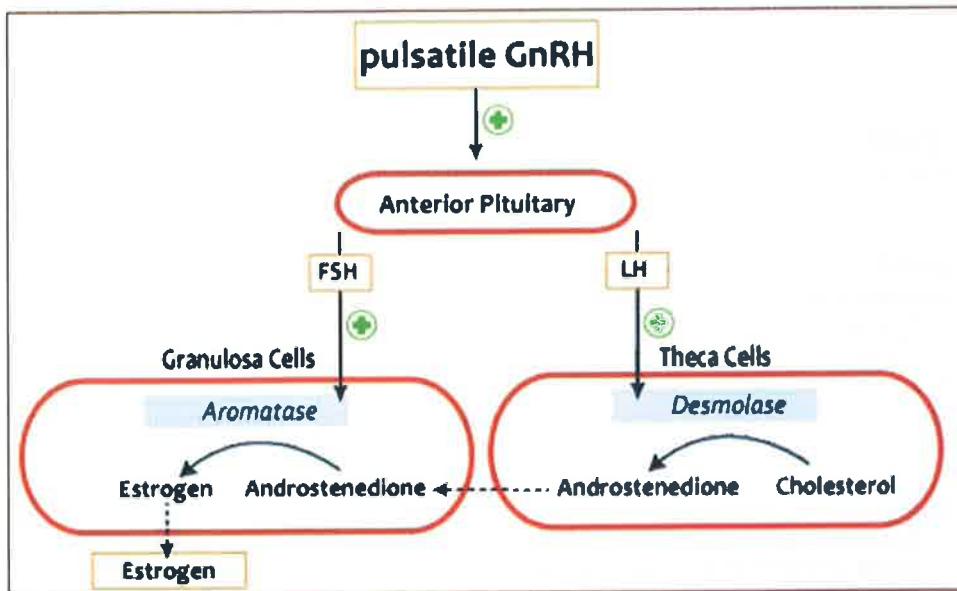
- ↑ Triglycerides and cholesterol (due to increased lipolysis and fat utilization)

↑ SHBG (Sex hormone-binding globulin) and corticosteroid-binding globulin

Beta-HCG has a degree of thyroid stimulating activity → ↓ TSH. No intervention is needed

Physiological effects of LH, FSH, and sex hormones

- ♀: Ovaries
 - FSH: follicular maturation → ↑ estrogen
 - LH: ↑ estrogen, **ovulation**, and ↑ progestrone
- ♂: Testicles
 - FSH: production of sperm, ↑ **inhibin**
 - LH: stimulation of Leydig cells → ↑ **production of testosterone**



Dihydrotestosterone (DHT)

Composition

- Testosterone is a steroid hormone and can be converted to oestradiol.

Production

- LH stimulates testosterone production and FSH spermatogenesis

Binding

- It binds to **intracellular receptors** and is mostly bound to **sex-hormone binding globulin (SHBG)**

Conversion

- Testosterone converted to dihydrotestosterone (**DHT**) in the body by the enzyme **5 α -reductase**. DHT is a more active compound than testosterone.
- The absence of **5 α -reductase** or the absence of **DHT receptors** leads to testicular feminisation.

Function

- During fetal development and early life: differentiation of the penis, scrotum, and prostate.
- expression of male secondary sex characteristics
- During late adulthood: prostate growth, male pattern baldness, and sebaceous gland activity.

Deficiency

- $\rightarrow \downarrow$ **testosterone is due to either:**
 - $\Rightarrow \downarrow$ free level due to \downarrow production (Leydig and pituitary dysfunction) (Lead to \uparrow synthesis of SHBG)
 - * increasing age: total testosterone concentrations fall slightly, and free testosterone fall more.
 - $\Rightarrow \downarrow$ activity at receptor often due to androgen receptor deficiency (5 α -reductase deficiency).

- ⇒ Patients with **5α-reductase deficiency** will have ambiguous genitalia at birth until they reach puberty, when the testosterone surge causes growth of external male genitalia, however, these patients are otherwise healthy. Individuals with this deficiency sometimes change their gender role in adolescence.
 - **obesity** (hyperinsulinaemia of obesity → ↓SHBG levels → ↓testosterone (*low SHBG and normal free testosterone*)

Evaluation

- Initial evaluation: serum testosterone in the early morning, fasting.
- Testosterone levels vary according to the degree of binding to albumin and SHBG: (↑SHBG → ↑total testosterone - when testosterone production is low-).
- The **equilibrium dialysis method** is most useful for measurement of **free testosterone** (not bound to protein)
- If the testosterone is low:
 - ⇒ measurement of **LH** and **FSH** to determine if the hypogonadism is primary or secondary. **If secondary** → assessment of other pituitary hormones.
 - ⇒ If the patient has **multiple pituitary hormonal deficiencies** and/or if the testosterone is **less than 200 ng/dL**, we suggest **MRI of the sella**.

Testosterone therapy

- **Indications**
 - ⇒ hypogonadal men to induce and maintain secondary sex characteristics and correct symptoms of testosterone deficiency.
 - ⇒ Older men (>65 years) with age-related decline in testosterone concentration:
 - routinely prescribing testosterone therapy is not recommended
 - **In symptomatic** (such as low libido or unexplained anemia) and consistently and unequivocally low morning testosterone, testosterone therapy may be offered on an individualized basis after discussion of the potential risks and benefits.
 - **HIV-infected men with weight loss and low testosterone** (when other causes of weight loss have been excluded) to induce and maintain body weight and lean mass gain.
- **Target**
 - ⇒ For patients receiving **testosterone enanthate**, the **testosterone level** should be **between 400 and 700 ng/dL** at about **half-way between administrations** (one week after injection) which are generally given every two weeks.
- **Which type of testosterone therapy is most likely to result in an increase in dihydrotestosterone level?**
 - ⇒ Dihydrotestosterone levels increase with the use of a testosterone **scrotal patch** due to the high concentration of **5α-reductase in genital skin**. Levels may return to normal after discontinuation; however, they often remain elevated.
- **Benefits of testosterone treatment**
 - ⇒ ↑sexual interest and activity, slight improvement in walking, slight improvement in mood, ↑ hemoglobin, and ↑ bone mineral density (BMD).
 - ⇒ No change in energy or cognition is expected.
- **Side effects**
 - ⇒ Erythrocytosis leading to **elevated haematocrit**
 - Haematocrit should be measured 3-6 months after initiating therapy and yearly thereafter.
 - Guidelines suggest that if haematocrit is increased and no other underlying cause is found, the dose should be down-titrated.
 - ⇒ PSA
 - Androgen replacement therapy is contraindicated in patients with prostate cancer and breast cancer.

- **Urological consultation is recommended if:**
 - ⇒ ↑PSA > 1.4 ng/mL within a 12-month period,
 - ⇒ a PSA velocity > 0.4 ng/mL/year using the level after 6 months of testosterone therapy as the reference
 - ⇒ abnormality on digital rectal examination, or
 - ⇒ an I-PSS score of greater than 19.

Polycystic ovarian syndrome (PCOS)

Polycystic ovarian syndrome - ovarian cysts are the most consistent feature

Infertility in PCOS - clomifene is superior to metformin

Incidence

- affect between 5-20% of women of reproductive age.

Aetiology

- not fully understood
- **Both hyperinsulinaemia and high levels of luteinizing hormone** are seen in PCOS

Features

- Oligo/amenorrhoea 70%
- hirsutism, acne (due to hyperandrogenism) 60%
- obesity 35%
- subfertility and infertility 30%.
 - ❖ Chronic anovulation is the mechanism for infertility
- **acanthosis nigricans** (due to insulin resistance)
- psychological symptoms
- Clitoromegaly is seen occasionally in PCOS but is normally associated with very high androgen levels. **If clitoromegaly is found, then further investigations to exclude an ovarian or adrenal androgen secreting tumour are required.**

Investigations

- pelvic ultrasound: multiple cysts on the ovaries
 - ⇒ transvaginal ultrasound is said to have 91% diagnostic sensitivity
 - ⇒ The presence of more than eight follicular cysts of less than 10 mm and increased ovarian stroma is sufficient to make the diagnosis.
- FSH, LH, prolactin, TSH, and testosterone are useful investigations:
 - ⇒ **FSH will be normal or low, while LH will be elevated.**
 - Increased LH causes hyperplasia of ovarian theca cells.
 - Increased LH causes increased testosterone and androstenedione
 - ⇒ **Raised LH: FSH ratio is a 'classical' feature** but is no longer thought to be useful in diagnosis.
 - LH/FSH ratio is normally about 1:1 in premenopausal women, but with PCOS a ratio of greater than 2:1 or 3:1 may be considered diagnostic.
 - ⇒ Prolactin may be normal or mildly elevated.
 - 10% of patients with PCOS have hyperprolactinaemia,
 - elevation in prolactin due to the low oestrogen stimulating GnRH, which in turn stimulates the anterior pituitary hormones including prolactin.

- However, the elevation in prolactin in PCOS rarely exceeds 1000 mU/l.
- ⇒ **Testosterone may be normal or mildly elevated** however, **if markedly raised consider other causes**
 - **The appropriate initial biochemical investigation**
 - Normal or elevated testosterone, but with a low sexhormone-binding globulin (SHBG) level, resulting in a high free androgen index.
- ⇒ **Sex hormone-binding globulin (SHBG) is frequently low**
 - (SHBG) is a transporter protein that binds to both testosterone and oestradiol;
 - it is reduced in insulin resistance, which is common in (PCOS).
 - (SHBG) is low in 50%, due primarily to hyperinsulinaemia.
 - The reasons include that androgens reduce the globulin production, whereas oestrogen promotes production.
 - Many women with PCOS have a high-normal or even a normal total testosterone, but a low SHBG because they have insulin resistance.
- ⇒ **hyperestrogenism**
 - Increased androstenedione/testosterone in PCOS can be peripherally converted in adipose tissue to **estrone** by aromatase.
 - increased circulating levels of estrone → endometrial hyperplasia which is a precursor to endometrial carcinoma
- **Impaired glucose tolerance**
 - ⇒ **hyperinsulinaemia** (insulin resistance → high circulating insulin levels due to peripheral insulin resistance).
 - ⇒ Up to 40% of women with PCOS have impaired glucose tolerance,
 - ⇒ up to 10% develop frank Type 2 diabetes mellitus

long term complication of PCOS:

- **risks of diabetes** (due to peripheral insulin resistance),
- sleep apnoea,
- **endometrial cancer**,
- mental health disorders.

Diagnostic criteria

- According to the Rotterdam Consensus, **two** of the following three criteria are required for the diagnosis of the PCOS:
 1. oligo-/anovulation
 2. hyperandrogenism
 - clinical (hirsutism or less commonly male pattern alopecia) or
 - **biochemical (raised free androgen index or free testosterone)**
 3. polycystic ovaries on ultrasound.

Management

- **General**
 - ⇒ Weight reduction: **the gold-standard treatment for PCOS**. A loss in weight of only 5% reduces hirsutism by up to 40%.
- **For associated hirsutism**
 - **Dianette® (cyproterone acetate) combined oral contraceptive pill (COC) is the most effective**
 - **if doesn't respond to COC then topical eflornithine may be tried**
 - Spironolactone, flutamide and finasteride may be used for its anti-androgenic properties

- For infertility

- ⇒ Initial step → weight loss
- ⇒ First-line drug: Anti-oestrogen therapies such as **clomifene** → the most effective treatment
 - work by occupying hypothalamic oestrogen receptors without activating them. This interferes with the binding of oestradiol and thus prevents negative feedback inhibition of FSH secretion
- ⇒ Second-line drug: Metformin is also used, either combined with clomifene or alone, particularly in patients who are obese but is not a first line treatment
- ⇒ Gonadotrophins: usually reserved for patients who are resistant to clomifene

MRCPUK-part-1-May 2009 exam: H/O infertility with PCOS. Apart from advising her to lose weight, which intervention is most effective in increasing her chances of conceiving?

Clomifene (if clomifene – the first line - is not an option, metformin – the second line - is the right answer)

September 2009 exam: Which finding is most consistently seen in polycystic ovarian syndrome? **Ovarian cysts on ultrasound**

MRCPUK-part-1-January 2012 exam: What is the mechanism of action of metformin in PCOS? **Increases peripheral insulin sensitivity**

Hirsutism

Hirsutism is often used to describe androgen-dependent hair growth in women
Hypertrichosis used for androgen-independent hair growth

Definition

- Excessive male pattern hair growth in women (e.g., on the chin, above the upper lip, and around the umbilicus)

Causes

- Idiopathic (the most common): normal menstrual cycle, normal serum androgen, , and no identifiable cause hirsutism.
- Polycystic ovarian syndrome is **the most common identifiable causes of hirsutism**
- Excess androgen (10% of cases): hirsutism, acne, menstrual dysfunction, alopecia.
 - ⇒ Cushing's syndrome
 - ⇒ congenital adrenal hyperplasia
 - ⇒ androgen therapy
 - ⇒ obesity: due to peripheral conversion oestrogens to androgens
 - ⇒ androgen secreting ovarian tumour
- Drugs

Assessment of hirsutism

- Mild hirsutism and normal menses → do not require laboratory workup and can be treated empirically.
- Moderate or severe symptoms → early morning **total testosterone** level
 - ⇒ if moderately elevated, it should be followed by a plasma **free testosterone** level.
 - ⇒ A total testosterone level greater than 200 ng per dL (6.94 nmol per L) should prompt evaluation for an androgen-secreting tumor.

- Testing for endocrinopathies and neoplasms, such as polycystic ovary syndrome, adrenal hyperplasia, thyroid dysfunction, Cushing syndrome, and androgen-secreting tumors.

Management

- Advise weight loss if overweight
- Hair removal (Shaving)
- Pharmacologic measures
 - ⇒ Combined oral contraceptive pills: **first-line pharmacologic treatment**
 - ⇒ Facial hirsutism: topical eflornithine - contraindicated in pregnancy and breast-feeding
 - ⇒ Treatment response should be monitored for at least six months before making adjustment.

Hypertrichosis

Definition

- excessive **hair growth above the normal** for the age, sex and race of an individual, in contrast to **hirsutism**, which is excess hair growth **in women** following a male distribution pattern.

Causes

- Drugs:
 - ⇒ **phenytoin**
 - ⇒ **minoxidil** (antihypertensive vasodilator. also used to treat androgenic alopecia → slows hair loss and promotes hair regrowth)
 - ⇒ **ciclosporin**
 - ⇒ diazoxide
- Congenital hypertrichosis lanuginosa, congenital hypertrichosis terminalis
- Metabolic disorders
 - ⇒ thyroid dysfunction
 - ⇒ porphyria cutanea tarda
 - ⇒ anorexia nervosa

Treatment

- Hair removal

Amenorrhoea

Primary amenorrhoea

- **Definition:** failure to start menses by the age of **16** years
- **Causes**
 - ⇒ Turner's syndrome
 - ⇒ testicular feminisation
 - ⇒ congenital adrenal hyperplasia
 - ⇒ congenital malformations of the genital tract

Secondary amenorrhoea

- **Definition**
 - ⇒ absence of menses for more than **3** months (in women with previously regular cycles) or **6** months (in women with previously irregular cycles)
- **Causes**
 - ⇒ Pregnancy → most common cause of secondary amenorrhoea
 - ⇒ hypothalamic amenorrhoea (e.g. Stress, **excessive exercise**) → ↓ FSH

- **Weight-related amenorrhoea**

- ⇒ amenorrhoea can even be seen at the lower end of the normal range.
- ⇒ often seen in ballet dancers, who maintain a **low weight** and undergo periods of extreme physical exercise.
- ⇒ Gaining body weight to above the 50th centile for height normally results in the restoration of menstruation, but if this cannot be achieved oestrogen replacement might be considered.
- ⇒ polycystic ovarian syndrome (PCOS)
- ⇒ hyperprolactinaemia
- ⇒ premature ovarian failure → ↑ FSH
- ⇒ thyrotoxicosis (hypothyroidism may also cause amenorrhoea)
 - Hypothyroidism (↓ T3/T4 → ↑ TRH → ↑ prolactin → ↓ GnRH → ↓ estrogens)
- ⇒ Sheehan's syndrome
- ⇒ Asherman's syndrome (intrauterine adhesions)

Initial investigations

- exclude pregnancy with urinary or serum bHCG
- gonadotrophins: low levels indicate a hypothalamic cause whereas raised levels suggest an ovarian problem (e.g. Premature ovarian failure)
- prolactin
- androgen levels: raised levels may be seen in PCOS
- oestradiol
- thyroid function tests

Primary ovarian failure means that the patient never has a normal menstrual cycle, and has the **triad of**

1. amenorrhea,
2. hypergonadotropinism,
3. hypoestrogenism.

Premature ovarian failure

The history of prolonged cessation of menses with a normal weight, normal thyroid function tests and a history of coeliac disease is pointed to a diagnosis of premature ovarian failure

Criteria for diagnosis

1. age under 40 years
2. menopausal symptoms (including no or infrequent periods)
3. and elevated FSH levels on 2 blood samples taken 4–6 weeks apart.

Epidemiology

- occurs in around 1 in 100 women.

Causes

- idiopathic - the most common cause
- chemotherapy
- **autoimmune**
- radiation

Features

- secondary **prolonged amenorrhoea**
- infertility
- climacteric symptoms: hot flushes, night sweats

Investigations

- **raised FSH**, LH levels
- **↓ oestradiol**
- sex hormone releasing hormones would be elevated in an attempt to drive LH and FSH release.

Treatment

- Hormone replacement therapy (**HRT**) or a combined hormonal contraceptive to protect against osteoporotic fracture.
 - ⇒ HRT may have a beneficial effect on blood pressure when compared with a combined oral contraceptive
 - ⇒ both HRT and combined oral contraceptives offer bone protection
 - ⇒ HRT is not a contraceptive.
- Spontaneous recovery of fertility is unlikely (occurs in only 5%).

Menopause

Definitions

- Peri-menopause → aged **over 45**, **vasomotor symptoms** and **irregular periods**
- menopause → aged **over 45**, **no period** for at least **12 months**, not associated with a pathology and not using hormonal contraception.

Symptoms

- Usually preceded by 4–5 years of abnormal menstrual cycles.
- **vasomotor symptoms** (e.g. **hot flushes** and sweats): **most common**
- musculoskeletal symptoms (for example, joint and muscle pain)
- effects on mood (e.g. low mood)
- urogenital symptoms (e.g. vaginal dryness)
- Sexual difficulties (e.g. low sexual desire).
- Women with **obesity** tend to suffer from **fewer symptoms** in menopause due to **peripheral conversion of androgens to estrogen** in adipose tissue.
- Most symptoms will disappear spontaneously within 5 years after onset.

Consequences

- **↓ bone mineral density** → osteoporotic fractures.
- ischaemic heart disease,
- **↓ insulin sensitivity**
- **↑↑ thrombotic tendency**.
- **Increased possibility of developing Alzheimer's dementia**
 - ⇒ Oestrogen deficiency might play a role in the development of dementia.

Investigations

- ↓ estradiol, ↓ progesterone, ↓ inhibin B
- ↑ GnRH, ↑ FSH and ↑LH (↑↑FSH is specific for menopause)
- Vaginal pH > 4.5
- Lipid profile: ↑ total cholesterol, ↓ high-density lipoprotein (HDL)
- Testosterone and prolactin levels are within normal ranges (androstenedione is produced by ovarian stromal cells and the adrenal glands.)

Management

- **Vasomotor symptoms** → **hormone replacement therapy (HRT)**
 - ⇒ women with a uterus → oestrogen and progestogen
 - ⇒ Women without a uterus → Oestrogen alone.
- **Psychological symptoms** → **low mood or anxiety** → HRT & CBT
 - ⇒ women with low sexual desire → testosterone supplementation if HRT alone is not effective.
- **Urogenital atrophy** → vaginal oestrogen (including those on systemic HRT), also in whom systemic HRT is contraindicated.

The ovaries' failure to produce estrogen **begins in the late 30s** and progresses to the degree that most women have **near-complete loss of estrogen production by their mid-50s**.

Whereas taking estrogen alone increases the risk of endometrial cancer, taking both estrogen and a progestogen in combination, as in most birth control pills, decreases the risk.

All postmenopausal women above the age of 65 should be screened for osteoporosis (i.e., using the DEXA scan to measure bone mineral density).

Hormone replacement therapy (HRT)

Main indication for HRT: control of vasomotor symptoms

HRT: unopposed oestrogen increases risk of endometrial cancer

HRT: adding a progestogen increases the risk of breast cancer

- Hormone replacement therapy (HRT) involves the use of a small dose of oestrogen, combined with a progestogen (in women with a uterus), to help alleviate menopausal symptoms.

Unopposed oestrogen therapy is most appropriate for patient who had a hysterectomy and combined hormone replacement therapy (HRT) is unnecessary.

Indications

- vasomotor symptoms such as flushing, insomnia and headaches (The main indication)
- Premature menopause: should be continued until the age of 50 years. Most important reason is preventing the development of osteoporosis

Types

- Estrogen therapy: for women who have had a hysterectomy
- Estrogen plus progestin therapy: for women with a uterus

Advantages of hormone replacement therapy (HRT)

- improvement in menopausal symptoms
- protection against fractures of the wrist, spine, and hip secondary to osteoporosis.
- reduce incidence of colorectal cancer
- reduce incidence of Alzheimer's

Hormone replacement therapy and effects on bone mass

- Reduction in total-body bone mass **begins in women in their late twenties**
- This loss is accelerated at the menopause
- Both trabecular bone loss at the level of the vertebrae and cortical bone loss at the radius are prevented by oestrogen therapy
- The risk of osteoporotic fractures is reduced, but not eliminated, by oestrogen therapy
- If the uterus has been removed in a patient, there is no need for additional progesterone therapy
- The effect of oestrogens on bone loss may be reduced after 10 years of oestrogen therapy**

Adverse effects

- Cancer
 - Unopposed estrogen can result in endometrial hyperplasia → increased risk of endometrial cancer
 - Estrogen plus progestin therapy → increased risk of breast cancer
- Thromboembolism: Cardiovascular disease: coronary heart disease, **deep vein thrombosis**, pulmonary embolism, stroke

Selective Estrogen Receptor Modulators (SERMs)

Raloxifene

- Mechanism of action
 - estrogen **antagonist** in **breast** and **endometrium**
 - agonist** in bone to increase mineralisation
- Clinical use
 - osteoporosis in menopausal women**
 - breast cancer prevention in women high risk for breast cancer

- **Toxicity**
 - ⇒ ↑ risk of venous thromboembolism
 - ⇒ induces menopause → hot flashes

Tamoxifen

- **Mechanism of action**
 - ⇒ **mixed oestrogen-receptor antagonist and partial agonist** depending on the target tissue
 - ❖ estrogen **antagonist** in **breast**
 - ❖ estrogen **agonist** in **endometrium** and **bone**
- **Clinical use**
 - ⇒ estrogen and progesterone receptor positive **breast cancer**
 - ⇒ breast cancer prevention in women high risk for breast cancer
- **Toxicity**
 - ⇒ ↑ risk of venous thromboembolism
 - ⇒ ↑ **risk of endometrial cancer** secondary to agonist activity
 - ⇒ induces menopause → hot flashes

Androgen insensitivity syndrome

The testosterone which is in the male range, the history of hernias as a baby and absence of acne or secondary sexual hair are all pointers towards androgen insensitivity syndrome.

The presence of **breast development** in the **absence of secondary sexual hair**, with a history of **hernias** as a child is suggestive of a diagnosis of **androgen insensitivity syndrome**. It is likely that the hernias were related to **undescended testes**. The vagina is blind ended, and there are no ovaries.

Pathophysiology

- **X-linked recessive mutation** of the gene encoding the androgen receptor (AR gene) → Defects in the androgen receptor → end organ insensitivity to androgens. end-organ resistance to testosterone causing genetically male children (46XY) to have a female phenotype.
- Complete androgen insensitivity syndrome is the new term for testicular feminisation syndrome

Features

- Primary amenorrhoea
- Undescended testes causing groin swellings, **Cryptorchidism** (absence of one or both testes from the scrotum)
- External genitalia ranges from normal female to female with clitoromegaly, to under-developed male (hypospadias) → **Associated with abdominal hernias**.
- Breast development may occur as a result of **conversion of testosterone to oestradiol**
- Blind-ended vaginal pouch, uterine and fallopian tube agenesis (due to testicular anti-Mullerian hormone secretion)
- Scant or no pubic hair

Diagnosis

- High level of LH
 - ↑ Oestrogen
 - Normal/↑ testosterone levels (no virilization)
- Buccal smear or chromosomal analysis to reveal 46XY genotype

Management

- Counselling - raise child as female
- Bilateral orchidectomy (increased risk of testicular cancer due to undescended testes)
- Oestrogen therapy

Disorders of sex hormones

The table below summarises the findings in patients who have disorders of sex hormones:

Disorder	LH	Testosterone
Primary hypogonadism (Klinefelter's syndrome)	High	Low
Hypogonadotrophic hypogonadism (Kallman's syndrome)	Low	Low
Androgen insensitivity syndrome	High	Normal/high
Testosterone-secreting tumour	Low	High

Menstrual cycle

The menstrual cycle may be divided into the following phases:

	Follicular phase (proliferative phase) (from day 1 until day 14)	Luteal phase (secretory phase) (From day 15 until day 28)
Ovarian histology	<ul style="list-style-type: none"> • A number of follicles develop. • One follicle will become dominant around the mid-follicular phase 	<ul style="list-style-type: none"> • Corpus luteum
Endometrial histology	<ul style="list-style-type: none"> • Proliferation of endometrium 	<ul style="list-style-type: none"> • Endometrium changes to secretory lining under influence of progesterone
Hormones	<ul style="list-style-type: none"> • A rise in FSH results in the development of follicles which in turn secrete oestradiol • When the egg has matured, it secretes enough oestradiol to trigger the acute release of LH. This in turn leads to ovulation • Graafian follicle is a large mature tertiary follicle containing an oocyte that is ready to be ovulated. • Ovulation occurs 14 days before menses, regardless of cycle length. • oestradiol stimulates the growth of the endometrium. • Progesterone levels are low • FSH activates aromatase within 	<ul style="list-style-type: none"> • corpus luteum produces (3 hormones) estrogen, inhibin, and progesterone. • progesterone is significantly higher than in other phases of the menstrual cycle. • If fertilisation does not occur the corpus luteum will degenerate and progesterone levels fall

	Follicular phase (proliferative phase) (from day 1 until day 14)	Luteal phase (secretory phase) (From day 15 until day 28)
	<p style="color: red;">granulosa cells, increasing estradiol production.</p> <ul style="list-style-type: none"> The main hormone controlling the follicular phase is <u>estradiol</u>, secreted by <u>Granulosa cells</u>. 	
Cervical mucus	<ul style="list-style-type: none"> Following menstruation the mucus is thick and forms a plug across the external os Just prior to ovulation the mucus becomes clear, acellular, low viscosity. It also becomes 'stretchy' - a quality termed spinnbarkeit 	<ul style="list-style-type: none"> Under the influence of progesterone it becomes thick, scant, and tacky
Basal body temperature	<ul style="list-style-type: none"> Falls prior to ovulation due to the influence of oestriadiol 	<ul style="list-style-type: none"> Rises following ovulation in response to higher progesterone levels

Which hormone levels would be most likely to indicate the occurrence of ovulation?

→ Luteinising hormone

At which point in the menstrual cycle do progesterone levels peak?

→ Luteal phase

⇒ Progesterone is secreted by the corpus luteum following ovulation.

Which mechanism is most likely responsible for the missed period in early pregnancy?

→ Syncytiotrophoblast produces human chorionic gonadotropin (hCG), which stimulates progesterone production by the corpus luteum.

Hypogonadism

Primary hypogonadism (Hypergonadotropic hypogonadism)

if LH and FSH are not elevated a primary hypogonadism is excluded.

- Pathophysiology**
 - ⇒ gonadal insufficiency (\downarrow testosterone, \downarrow estrogen) → \uparrow gonadotropin secretion (\uparrow FSH and \uparrow LH) from the anterior pituitary (lack of negative feedback from the impaired gonads)
- Causes**
 - ⇒ Congenital abnormalities: (Primary gonadal insufficiency):
 - Turner syndrome (females)
 - Klinefelter syndrome (males)
 - androgen insensitivity syndrome
 - ⇒ Acquired diseases: (Secondary gonadal insufficiency) → (damage to Leydig cells or ovarian tissue):

- Medications (Radiation, chemotherapy, Ketoconazole, Glucocorticoids, toxins)
 - Autoimmune disease
 - Infections (**mumps**, tuberculosis)
 - **Tumour, infiltration (Testicular tumour)**
 - Chronic systemic illnesses (eg: Hepatic cirrhosis, Chronic renal failure)
 - Ageing: **Andropause** (\downarrow testosterone with age >50).
 - Primary testicular failure (**idiopathic failure**).
- **Investigations**
 - \Rightarrow \uparrow LH & FSH + \downarrow testosterone + \downarrow sperm count
 - \Rightarrow **Testicular ultrasound** (the most important investigation after blood hormones)

Secondary hypogonadism (hypogonadotropic hypogonadism)

In male patients with low libido have been found to have a low testosterone first line investigation should include **prolactin** and **LH** to assess for a central cause

- **Pathophysiology**
 - \Rightarrow \downarrow pituitary gonadotropins (\downarrow FSH and \downarrow LH) \rightarrow \downarrow testosterone and \downarrow estrogen
- **Causes**
 - \Rightarrow Genetic defects: (e.g., **Kallmann syndrome**, Prader-Willi syndrome, Gaucher disease)
 - \Rightarrow Hypothalamic and/or pituitary lesions due to: Neoplasm (e.g. prolactinoma, craniopharyngioma, astrocytoma)
 - \Rightarrow Malnutrition (e.g., anorexia nervosa)
 - \Rightarrow Chronic diseases (e.g., inflammatory bowel disease, hypothyroidism, cystic fibrosis, **diabetes** and obesity.)
- **Investigations**
 - \Rightarrow serum **testosterone** and **sperm count** are **subnormal** + **normal or reduced LH and FSH**
 - \Rightarrow **Prolactin level** (\uparrow Prolactin reduces LH and FSH)
 - \Rightarrow measure of **free testosterone** (as total testosterone can be low due to SHBG being decreased in obesity and with ageing).
 - \Rightarrow Pituitary MRI : the best image to exclude other pituitary pathology.

Clinical features

- **Delayed puberty**
- Developmental abnormalities with genitalia (undescended testes, hypospadias)
- Infertility (\downarrow sperm count), impotence, and/or \downarrow libido
- Secondary amenorrhea

Treatment

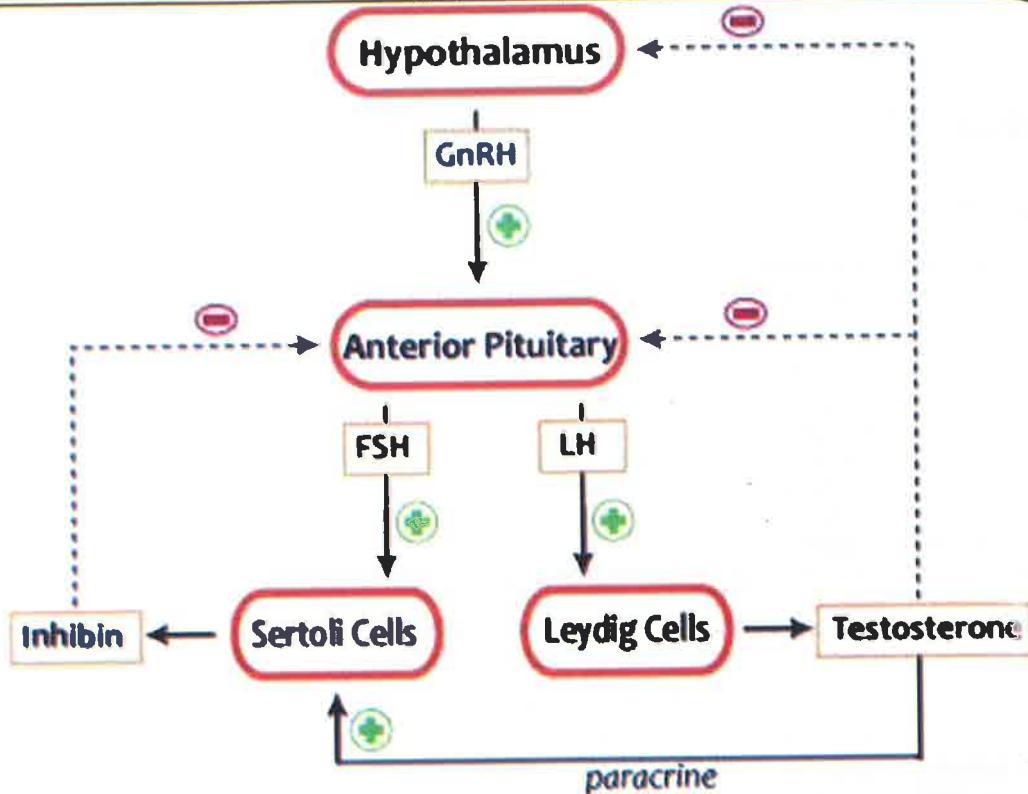
- Treat underlying cause: e.g., surgical excision of tumors, pharmacotherapy for prolactinomas
- Hormone replacement therapy

Poor ability to concentrate is most consistent with post-pubertal loss of testicular function, whereas (High-pitched voice, Gynecomastia, Disproportionately long arms and legs, Scant pubic and axillary hair) are most consistent with hypogonadism that develops before puberty.

Tip to remember

Testosterone and LH levels can help distinguish between different causes of abnormal sexual development:

- 1- High testosterone and high LH: defective androgen receptor (androgen insensitivity syndrome)
- 2- High testosterone and low LH: testosterone-secreting tumor
- 3- Low testosterone and high LH: primary hypogonadism
- 4- Low testosterone and low LH: hypogonadotropic hypogonadism

**Delayed puberty**

The first visible sign of puberty in males is testicular enlargement, while in females it is breast development.

Definition

- Absent or incomplete development of secondary sex characteristics by the age of 14 years in boys or 13 years in girls

Causes

- **Constitutional delay of growth and puberty (normal variants of growth): the most common cause of delayed puberty**
- Primary/ hypergonadotropic hypogonadism: e.g. Klinefelter's and Turner's syndromes.
- Secondary/ hypogonadotropic hypogonadism: causes
 - ⇒ Genetic defects: (e.g., Kallmann syndrome, Prader-Willi syndrome, Gaucher disease)
 - ⇒ Malnutrition (e.g., anorexia nervosa)
 - ⇒ Chronic diseases (e.g., inflammatory bowel disease, hypothyroidism, cystic fibrosis)

Delayed puberty with short stature	Delayed puberty with normal stature
Turner's syndrome	polycystic ovarian syndrome
Prader-Willi syndrome	androgen insensitivity
Noonan's syndrome	Kallman's syndrome Klinefelter's syndrome

Features

- **Signs of delayed puberty in girls include:**
 - ⇒ Absence of breast development by age 14 years
 - ⇒ Pubic hair absent by age 14
 - ⇒ More than five years between the start and completion of breast growth
 - ⇒ **Menarche has not occurred by age 16.**
- **Signs of delayed puberty in boys include:**
 - ⇒ No testicular enlargement by age 14 years
 - ⇒ Pubic hair absent by age 15
 - ⇒ More than five years between the start and completion of growth of the genitalia.

Diagnosis

- **Primary hypogonadism** → ↓gonadal hormones (testosterone in boys and estradiol in girls) + ↑luteinizing hormone (LH) and follicle-stimulating hormone (FSH).
- **Secondary hypogonadism** → ↓hypothalamic gonadotropin-releasing hormone (GnRH) → low to normal LH and FSH → ↓gonadal hormones
- **Constitutional delay** is usually assessed using a **bone age assessment** (radiography of the hand and wrist) and measuring the patterns of ossification at the epiphyses of the bones of the hands → delayed bone age.

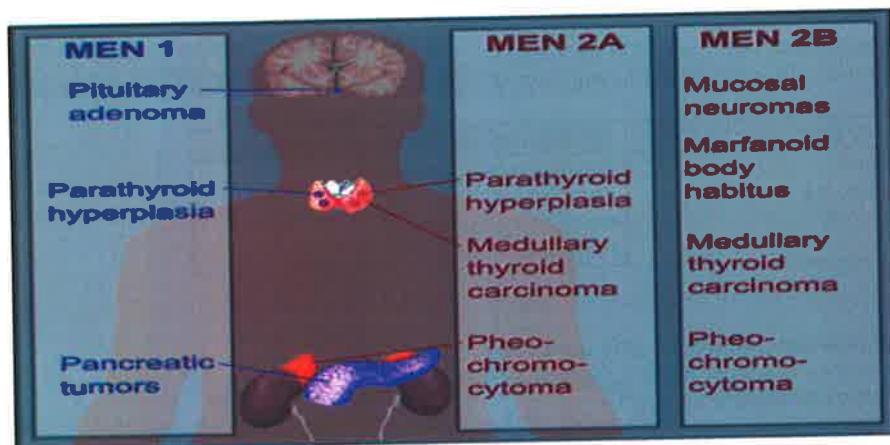
Management

- Constitutional delay: Observation
- Organic delay: Sex-steroid therapy to induce puberty + lifelong hormone replacement therapy after puberty

Multiple endocrine neoplasia

Genetic inheritance

- **Autosomal dominant** disorder, high penetrance
- The table below summarises the three main types of multiple endocrine neoplasia (MEN)



Type 1 multiple endocrine neoplasia (MEN 1)

- a defect in the gene **MEN1**, a tumor-suppressor gene found on **chromosome 11** that codes for **menin** protein.
- For MEN1, remember the triad of three **Ps**, which includes **pituitary**, **parathyroid**, and **pancreatic** tumors.
 - ⇒ Pituitary tumors → ↑ prolactin → galactorrhea, decreased libido, or infertility.
 - ⇒ Hyperparathyroidism is the most common manifestation in MEN 1 (**occurs in 90% of cases**) → hypercalcemia → constipation, kidney stones, polyuria, and polydipsia.
 - ⇒ The pancreas is the second most commonly involved organ in MEN 1.
 - **60% of pancreatic endocrine tumours are gastrinomas (most common)** → ↑ gastrin (Zollinger-Ellison syndrome) → recurrent peptic ulcers.
 - insulinooma → recurrent episodes of hypoglycemia, leading to confusion, dizziness, or loss of consciousness.
 - endoscopic ultrasound of the pancreas is the most sensitive modality for the detection of an insulinooma.
- The single most useful investigation to monitor patients with MEN 1 → Serum calcium
- Diagnosis → **genetic testing**
- Management
 - ⇒ Genetic screening for first-degree relatives
 - ⇒ Pituitary prolactinomas → cabergoline, a dopamine agonist
 - ⇒ Hyperparathyroidism → partial or total surgical parathyroidectomy
 - ⇒ Gastrinomas with peptic ulcer disease → proton pump inhibitor drugs.

MEN1 = three Ps
Pituitary, Parathyroid, Pancreas

Type 2 multiple endocrine neoplasia (MEN 2)

- MEN2A and MEN2B are both due to **mutations in the gene RET**. This is a proto-oncogene found on **chromosome 10** that codes for a receptor tyrosine kinase.
- A gain-of-function mutation in the **RET proto-oncogene** makes it an oncogene, which causes the uncontrolled cell division seen in cancer.
- **MEN-2 is strongly associated with a family history of unexplained death in childbirth**
- **Subtypes**
 - ⇒ **MEN Type 2a**
 - MEN type 2A includes two **P**s and one **M**—parathyroid tumors and **pheochromocytoma**, combined with **medullary thyroid carcinoma**.
 - pheochromocytoma →↑catecholamines such as epinephrine →hypertension and often intermittent episodes of headaches, palpitation, pallor caused by vasoconstriction, and heavy sweating.
 - **Medullary thyroid cancer** often metastasized at presentation →hoarseness
 - **Serum calcitonin** levels should be obtained in the workup for medullary thyroid cancer.
 - **young-onset hypertension with feature of hyperparathyroidism (\uparrow Ca & ↓ P)** → **MEN Type 2a**
 - ⇒ **MEN-2b**
 - MEN-2b present earlier than 2a
 - MEN type 2B is associated with a single **P** and two **M**s—**pheochromocytoma**, **medullary thyroid carcinoma**, and **mucosal neuromas**.
 - **Mucosal neuromas** (benign tumors) develop in the mouth, eyes, and submucosa of almost all organs in the first decade of life and appear in 100% of patients with MEN2B (yellowish-white painless nodules on the lips or tongue, sclera, or eyelids).
 - **Marfanoid habitus** → long limbs, wide arm span, and hyperlaxity of joints.

MEN2A = two P's and one M

Parathyroid, Pheochromocytoma, Medullary thyroid carcinoma

MEN2B = one P and two Ms

Pheochromocytoma, Medullary thyroid carcinoma, Mucosal neuromas

- **Diagnosis** → genetic testing
- **Management**
 - ⇒ Genetic screening for first-degree relatives
 - ⇒ All first-degree relatives who screen positive for the RET mutation should undergo prophylactic thyroidectomy given the very high risk of medullary thyroid cancer.
 - ⇒ For underlying phaeochromocytoma.
 - **full alpha blockade with an agent such as phenoxybenzamine is essential**
 - **the most appropriate additional medication to control blood pressure is → phenoxybenzamine**
 - Beta blockade without first alpha blocking raises the possibility of rebound hypertension due to unopposed action of the alpha vasoconstrictors; as such it is inadvisable to consider bisoprolol or atenolol.
 - **The pheochromocytoma puts the patient at greatest risk, and therefore should be removed before other surgical procedures are performed.**

- Annual testing of calcium and PTH from the age of 10 is recommended for child with family history of MEN-2

Which of the manifestations of MEN-2 has the most malignant potential?

C cell hyperplasia

Which finding in a blood test will be the most characteristic in (MEN 2B) patient?

- Elevated metanephrenes → phaeochromocytoma
- Elevated Calcitonin* → Medullary thyroid cancer (used for screening, prognosis and monitoring)

Multiple endocrine neoplasia type II is due to mutation in which sort of receptor?

Membrane-bound tyrosine kinase receptor

What is the single most useful investigation to monitor patients with MEN 1?

Serum calcium

Multiple endocrine neoplasia

MEN 1	3 "P"s = Parathyroid, Pancreas, Pituitary gland
MEN 2A	1 "M", 2 "P"s = Medullary thyroid carcinoma, Pheochromocytoma,
MEN 2B	2 "M"s, 1 "P" = Medullary thyroid carcinoma, Marfanoid habitus/Multiple neuromas, Pheochromocytoma

Autoimmune polyendocrinopathy syndrome (APS) (Polyglandular syndrome)

Type	Polyglandular syndrome type 1	Polyglandular syndrome type 2 Also called (Schmidt's disease)
inheritance	autosomal recessive caused by mutation of AIRE1 gene on chromosome 21	polygenic inheritance linked to HLA DR3/DR4.
Prevalence	Rare	More common
Age of presentation	Usually begins in childhood.	Usually begins in adult (most cases occurring between age 20 and 40 years)
Feature	<p>Most common</p> <ul style="list-style-type: none"> Mucocutaneous candidiasis (100%) (typically first feature as young child) Hypoparathyroidism (90%) Adrenal insufficiency (60%) <p>Less common</p> <ul style="list-style-type: none"> Other autoimmune diseases gonadal failure Primary hypothyroidism 	<p>Most common</p> <ul style="list-style-type: none"> Adrenal insufficiency (100%) (the initial manifestation) Hypothyroidism Type-1 diabetes <p>Less common</p> <ul style="list-style-type: none"> Other autoimmune diseases Gonadal failure Diabetes insipidus (rare)
Diagnosis	<p>2 out of 3 needed:</p> <ul style="list-style-type: none"> chronic mucocutaneous candidiasis (100%) primary hypoparathyroidism (90%), Addison's disease (60%) 	Patients have Addison's disease plus either: type 1 diabetes mellitus or autoimmune thyroid disease. No Hypoparathyroidism

- **Tryptophan hydroxylase autoantibodies** may be found in autoimmune polyendocrine syndrome associated with an autoimmune malabsorption.