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Chapter 1

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 1

Endocrinolog & Metabolism

• 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.

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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)

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Endocrinolog & Metabolism 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

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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

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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 (onetime 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

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• 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 DS 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, ↓↓calcium absorption from the gut,
 ↑↑urinary calcium excretion,
• The dose? The risk ↑↑ 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. age > 65 years or H/O previously fragility fracture → 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. age < 65 years → 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):

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 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

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

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• 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

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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
 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 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 alendronic 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.)

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Adrenal gland conditions Adrenal gland: Basics

Adrenal cortex (mnemonic GFR - ACD) • zona Glomerulosa (on outside): mineralocorticoids, mainly Aldosterone • zona Fasciculata (middle): glucocorticoids, mainly Cortisol • zona Reticularis (on inside): androgens, mainly Dehydroepiandrosterone (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-uptaked 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-Omethyl 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 • ♀ > ♂

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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 (7µg/ml, 18umol/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

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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 Appetite, Blood pressure, Insulin resistance, Glucose production, and decreased Fibroblasts, Immunity, and Bone 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)

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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

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_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 androgensecreting 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)

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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).

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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):
5. sustained HTN (>150/100 in 3 separate measurements taken on different days;
6. HTN resistant to 3 antihypertensive drugs;
7. HTN controlled with ≥ 4 medications;
8. HTN + low potassium
9. HTN + adrenal incidentaloma;
10. HTN + sleep apnea;
11. HTN + family history of early-onset hypertension or stroke before age 40;
12. 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 Bilateral idiopathic adrenal hyperplasia is the most common cause of primary hyperaldosteronism

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 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-tocortisol 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 reninangiotensin 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

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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.
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. Loss of normal circadian rhythm of aldosterone secretion (normally: lowest around midnight, and highest in early morning)

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)
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have more severe hypertension, hypokalemia, and higher urinary aldosterone than IAH. decrease in the aldosterone level with upright posture preserved of normal circadian rhythm of aldosterone secretion

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Adverse effects • General side effects Metabolic and electrolyte imbalances, such as hyperkalemia (most common), hyponatremia, and metabolic acidosis, can lead to cardiac arrhythmias Gastrointestinal disturbances (nausea, vomiting, diarrhea) • Spironolactone-specific side effects: endocrine disturbances Men: antiandrogenic effects (e.g., gynecomastia, erectile dysfunction) Women: amenorrhea

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Adrenal incidentaloma

Definition • asymptomatic adrenal mass detected on imaging not performed for suspected adrenal disease. Prevalence • occur in up to 10% of the population with imaging Approach • determine whether the incidentally discovered adrenal mass is:
 Malignant Functioning and associated with excess hormonal secretion.

Differential diagnosis • Phaeochromocytoma (10–15%). • Adrenocortical carcinoma (5–12%). • Adrenal myelolipoma (5–10%). • Metastasis (2–10%; most prevalent breast, lung, kidney). • Cortisol-secreting adrenal adenoma causing Cushing’s syndrome or subclinical Cushing’s syndrome (5%). • Adrenal cysts (5%). • Ganglioneuroma (4%).

Investigations

Adrenal mass on CT:
• Low density (Hounsfield Units ≤10) = high fat content = benign • High density (>20 HU) = suspicious (phaeochromocytoma/adrenocortical carcinoma/metastasis but also lipid-poor adenoma)

• Exclude malignancy → Noncontrast CT
 If the mass is homogeneous and low density (Hounsfield Units ≤10) (lipid-rich) and smaller than 4cm → benign adrenal mass → no further imaging is required
 Surgery if there is any one of the following Evidence of a syndrome of hormonal excess attributable to the tumour The most important thing to exclude, particularly in view of any further intervention, is a phaeochromocytoma (plasma free metanephrines) as catastrophic consequences can ensue following anaesthesia or surgical intervention.

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 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 metanephrines (most sensitive and specific screening test) or alternatively urinary fractionated metanephrines (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 ≤50nmol/L (≤1.8µg/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.

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 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.

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• 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: 21β-hydroxylase deficiency (~ 95% of CAH)
 11β-hydroxylase deficiency (~ 5% of CAH) 17α-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 androstenedione, 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 11β-hydroxylase deficiency will present with increased blood pressure, hypokalemia and increased androgen levels, differentiating it from 17α-hydroxylase deficiency.

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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)

cortisol + ↑ ACTH + Ambiguous genitalia ↓ ↓Aldosterone +

↑ Aldosterone +

testosterone ↑ ↓ testosterone

21-α hydroxylase 17-α hydroxylase deficiency

deficiency

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CAH

↓ Aldosterone +

- ↑ testosterone

↑ 11-deoxycorticosterone

11-β hydroxysterone deficiency