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Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

- Ultrasound "U" classification of thyroid nodules Classification Criteria U1 (normal)

no nodules U2 (benign)

-

hyperechoic or isoechoic with a halo

cystic change with ring down artiifact (colloid)

microcystic or spongiform appearance

peripheral egg-shell calcification

peripheral vascularity U3 (indeterminate)

-

solid homogenous markedly hyperechoic nodule with halo (follicular lesions)

hypoechoic with equivocal echogenic foci or cystic change

mixed or central vascularity U4 (suspicious)

-

solid hypoechoic (compared with thyroid)

solid very hypoechoic (compared with strap muscles)

hypoechoic with disrupted peripheral calcification

lobulated outline U5 (malignant)

-

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.

Chapter 1

Endocrinolog & Metabolism

• 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:

1. Ionized/ free (~45%,active form): The most important form in regulation of body functions
2. Bound to albumin (~40%)
3. Bound to anions (~15%) Actions of the Hormones Involved in Calcium Homeostasis
   HORMONE EFFECT ON BONES Parathyroid hormone →↑Ca++, ↓PO4 levels in blood
   ↑Ca++resorption and PO4 excretion,
   activates 1-hydroxylation → ↑ conversion of 25hydroxycholecalciferol to 1,25dihydroxycholecalciferol Calcitriol (vitamin D) ↑Ca++,↑PO4 levels in blood
   ↑osteoclastic activity Indirect effects via ↑calcitriol from 1hydroxylation ↑osteoclastic activity ↑Ca++ and PO4 absorption Calcitonin causes ↓Ca++, ↓PO4 levels in blood when

hypercalcemia is present Inhibits osteoclast resorption Notes & Notes for MRCP
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EFFECT ON GUT EFFECT ON KIDNEYS ↑renal tubular reabsorption of Ca++ and PO4 No direct effects Promotes Ca++ and PO4 excretion

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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.

Hypercalcaemia

Definition • Corrected calcium of more than 2.6 mmol/l.

hyperparathyroidism →↑Ca++, ↓PO4 levels 90% of hypercalcemia are caused by primary hyperparathyroidism and li Thiazides cause hypercalcaemia, might unmask underlying primary hyperparathyroidism (PHPT), as they cause mild hypercalcemia by reducing urinary calcium excretion. 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)

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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

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Differentiate between hypercalcaemia in primary hyperparathyroidism and malignancy: • in primary hyperparathyroidism Parathyroid hormone is elevated or normal
 calcium level is often < 3 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 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 • Pyschic 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 (Ca++ >3.5 mmol/L) and symptomatic moderate hypercalcemia (Ca++ 3.0–3.5 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

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 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 hypercalcaemia (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 Ca2+ 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 recommend (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)

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• 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).

 ↓↓ 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 Magnesium deficiency causes hypocalcaemia

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• 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

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 ≤ 7.5 mg/dL (< 1.9 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

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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.

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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

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 PO4- also enter cells) Refeeding syndrome (PO4- also enters cells), Acute pancreatitis.
Replace magnesium before correcting hypokalaemia.
Hypomagnesaemia prevents potassium absorption

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• 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.

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Features General
• lack of appetite. • Lethargy • fatigue Neuromuscular hyper-excitability
• muscle weakness including fasciculations • changes in personality • paraesthesia • tetany • seizures

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 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 mmol/l intravenous replacement is commonly given. An example regime would be 40 mmol of magnesium sulphate over 24 hours •

> 0.4 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: Notes & Notes for MRCP
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Cardiac • arrhythmias (ECG features similar to those of hypokalaemia) typically QT prolongation. • exacerbates digoxin toxicity

Electrolytes • ↓Mg →↓PTH secretion + ↑PTH resistance → hypocalcaemia • Hypokalemia (in 40-60%) (↓Mg →↑renal potassium wasting)

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 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 hypercalcaemia. 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

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

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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: 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 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:
 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 Oversupplementation Granulomatous disorders (e.g., sarcoidosis): due to increased 1α-hydroxylase activation in epithelioid macrophages → increased 1,25-dihydroxyvitamin D synthesis
 Clinical features Hypercalcemia, hypercalciuria
 Loss of appetite Stupor

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 10µg 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

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 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

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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.

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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:

1. 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.
2. Decreased intestinal absorption chronic diarrhea malabsorption syndromes severe vomiting nasogastric (NG) tube suctioning Alcohol use disorder
3. 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
4. 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

oxygenated 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:

1. I.V therapy with dextrose-containing solutions or refeeding → ↑Glucose → ↑ insulin release → ↑ phosphate uptake by the cells
2. alcohol withdrawal → hyperventilation → acute respiratory alkalosis → intracellular alkalosis → stimulates intracellular phosphofructokinase →↑ glycolysis → movement of phosphate into cells.

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 Ca2+ absorption →↓Ca2+ → ↑PTH
CRF →↓phosphate excretion → hyperphosphatemia.
Causes of ↓Ca2+ : • 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 ca2+. occurs after years of secondary hyperparathyroidism PTH is raised, calcium is raised and so is phosphate, whilst eGFR is significantly deceased

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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 25hydroxycholecalciferol 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 inappropriately 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

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 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)

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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 Tscore 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.

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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

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 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 (& C)

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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

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