

# Hyper and hypocalcaemia

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# Learning Objectives

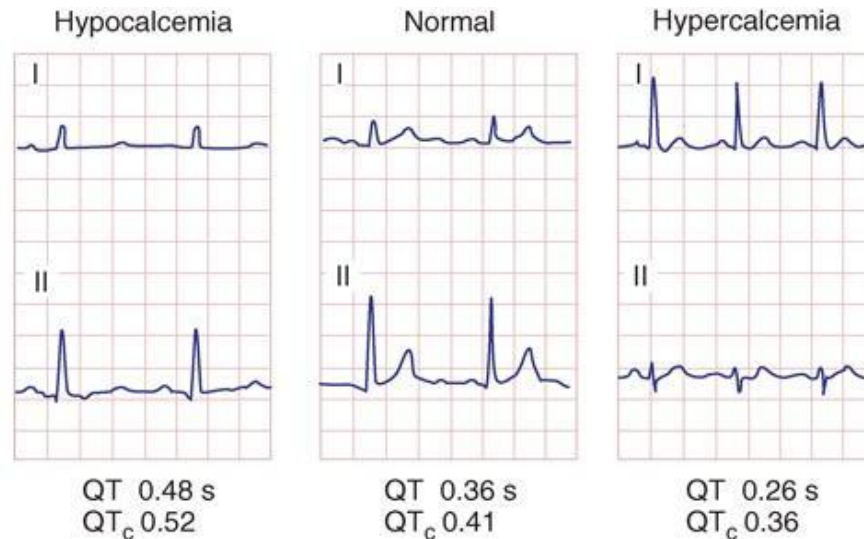
- Basic physiology of Ca regulation
- Case presentations
- Take home messages

# Calcium

- Total body calcium content ~1300g
  - 99% in bone
  - 1% intracellular
  - 0.1% extracellular
- Ca in blood :
  - 40% protein bound
  - 60% Ultrafilterable
    - 10% complexed to anions
    - 50% Ionised Ca

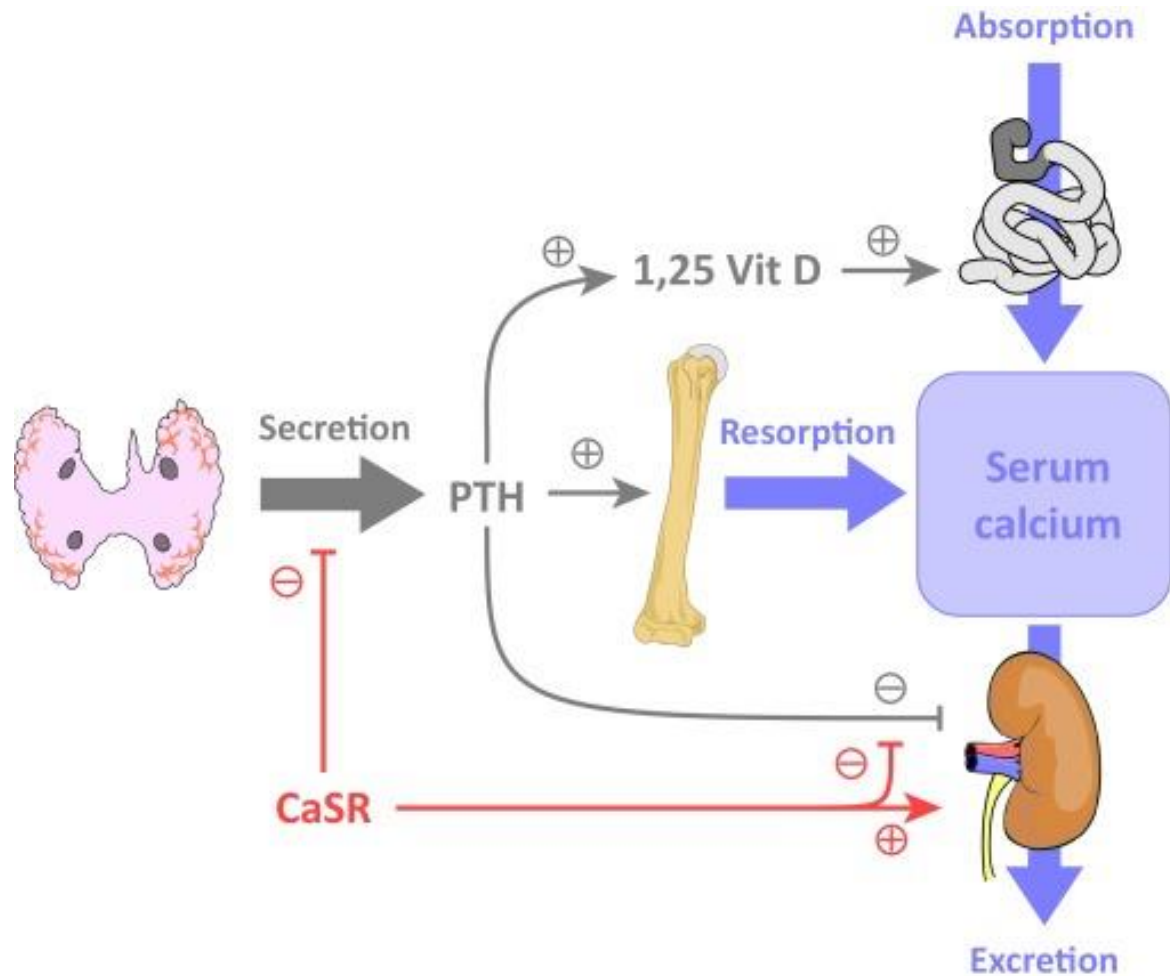
# What is Calcium for?

- Structural component of bone
- Vitally required for muscle function, especially cardiac:



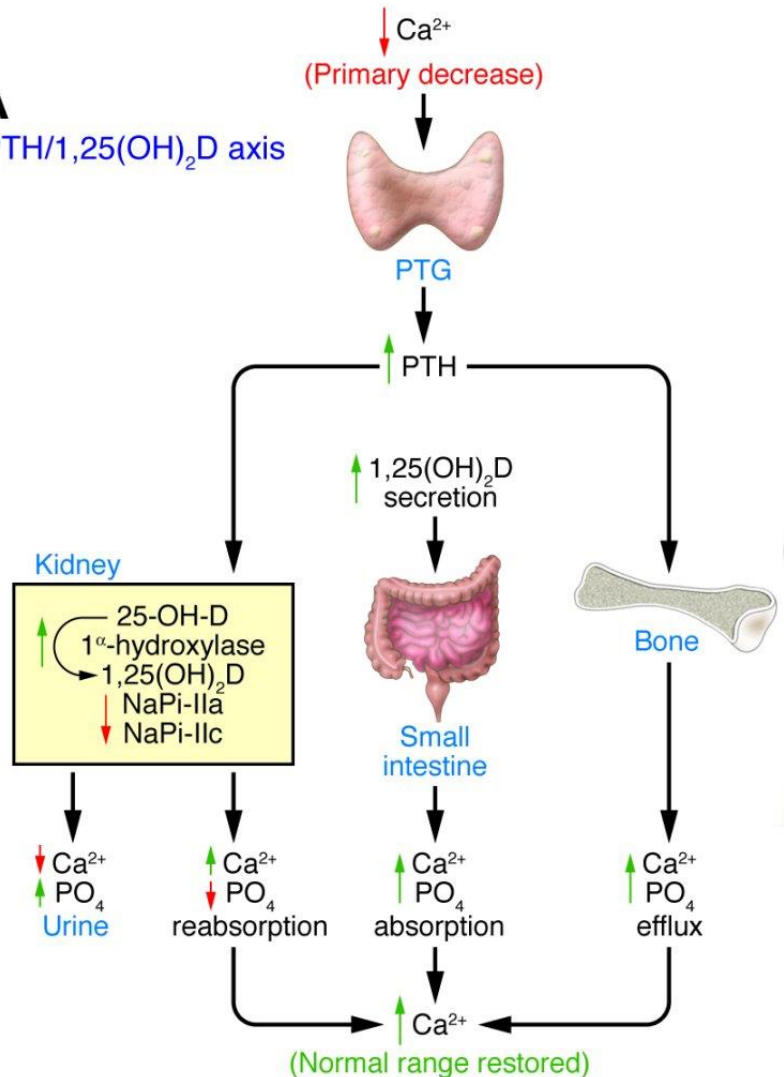
- Cellular functions (exocytosis etc.)

# Calcium is regulated

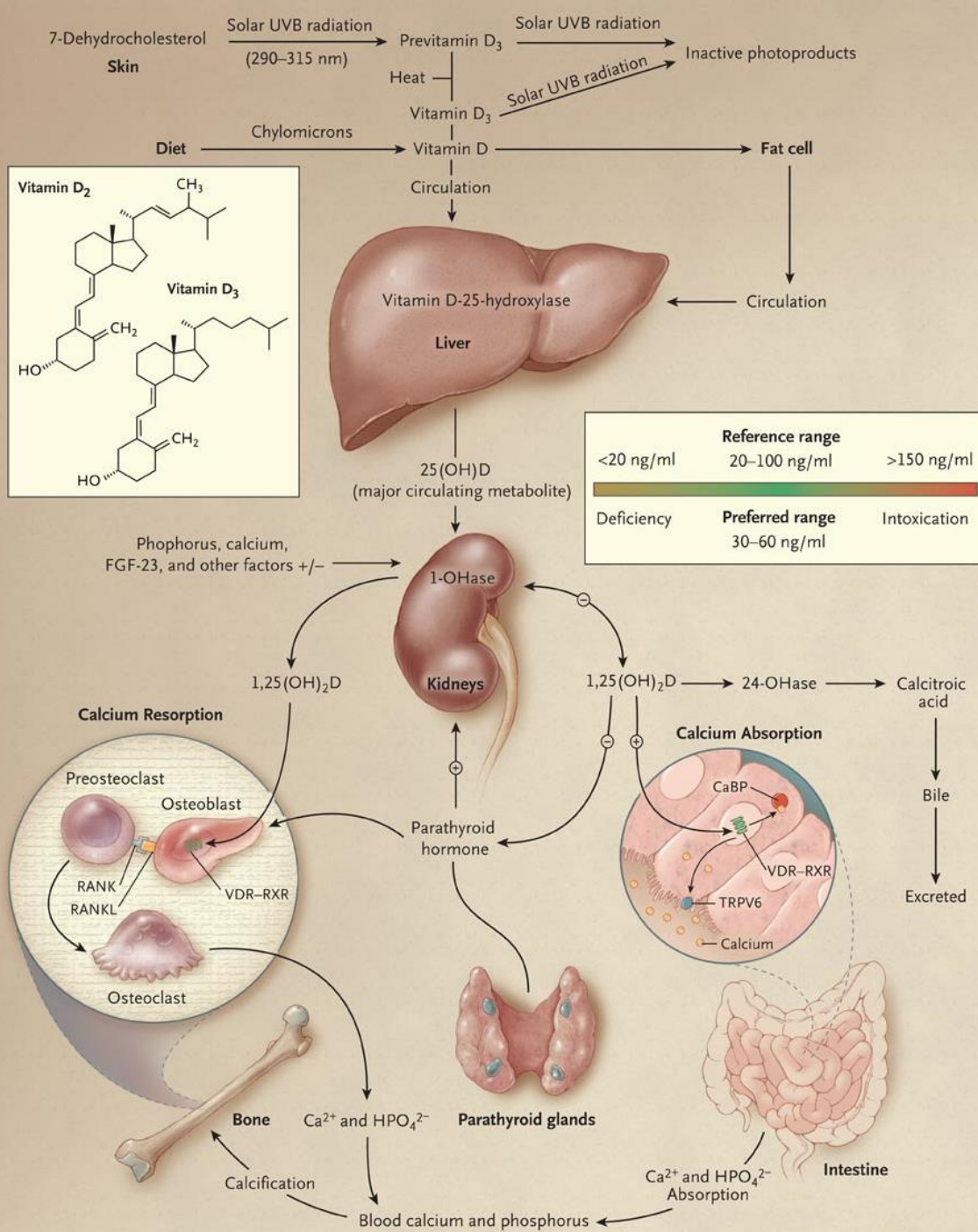


# Response to low Ca levels

**A**  
PTH/1,25(OH)<sub>2</sub>D axis



- PT glands secrete PTH
- $\uparrow$ Ca absorption in the intestine
  - Via  $\uparrow$ 1,25 vitamin D
- $\uparrow$ Ca efflux from bone
  - Via osteoclast activation
- $\uparrow$ Ca reabsorption from kidneys
  - Via  $\uparrow$ 1,25 vitamin D
  - Direct effect on Na/phosphate co-transporters  $\rightarrow$   $\downarrow$ Pi reabsorption



# Metabolism of Vitamin D

# Case 1

- 34 year old lady, 12 weeks pregnant
  - Vomiting
  - Routine bloods
    - Thyroid function normal
    - Corrected Calcium 3.05 mmol/L
- What do you need to do?



# Symptoms of hypercalcaemia

- Often asymptomatic
- ‘Bones’ – bone pain
- ‘Stones’ – kidney stones
- ‘Moans’ – depression and confusion
- ‘Groans’ – abdominal pain? Pancreatitis?

# Triaging Hypercalcaemia

PTH ↑	PTH ↓
Primary hyperparathyroidism	Malignancy
Familial hypocalciuric hypercalcaemia	Granulomas
	Endocrine causes
	Iatrogenic

PTH is the first test you will need

↓PO<sub>4</sub><sup>-</sup> suggests PTH or PTH-like action → ↑urinary loss

# What needs to be done next

- Assess patient for confusion and fluid status
- Obtain
  - U&E, repeat Ca, PTH and Vitamin D
  - TFTs and cortisol
  - Amylase
  - 24h urine collection for Ca and Cr

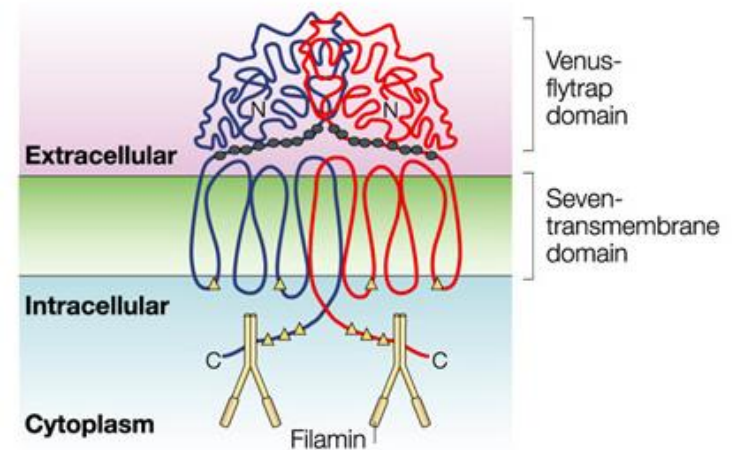
# Primary hyperparathyroidism

- 1/1000 prevalence
- 80% single gland, 20% multiple gland
- Familial
  - c. 1% cases
  - Think of this with young patients
  - Menin MEN-1 and familial isolated HPT
  - Ret MEN-2
  - Hrpt2 HPT-jaw tumour syndrome, associated with PT carcinoma

# Familial Hypocalciuric Hypercalcaemia

- Most commonly due to heterozygous loss of function in Ca sensing receptor (CaSR)
- $\uparrow$  Parathyroid set point for Ca
- $\uparrow$  reabs urinary Ca

- Asymptomatic  $\uparrow$ Ca,  
 $\uparrow$ PTH
- $\downarrow$ Ca in urine



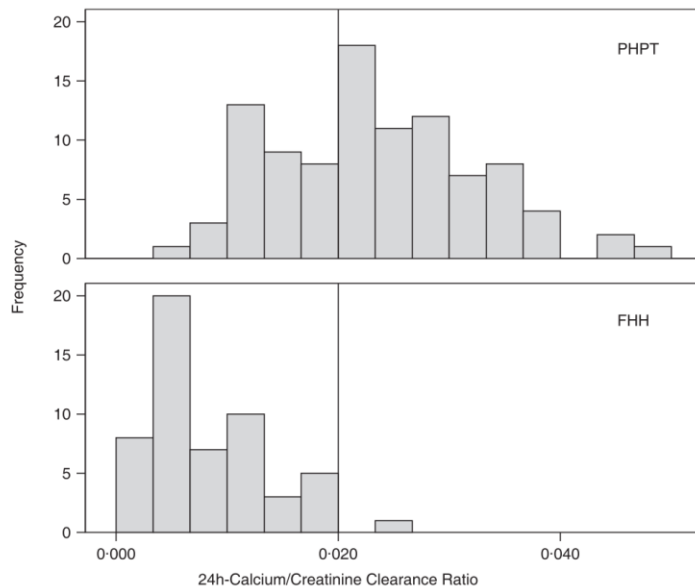
# How to distinguish PHPT vs FHH

- Corrected Calcium to Creatinine Ratio

$$= (U_{Ca} \times S_{Cr}) \div (S_{Ca} \times U_{Cr})$$

- Use 24 h urine collection

- Make sure units the same ( $\mu\text{mol}$  vs  $\text{mmol}$  for Cr)



Overlap between PHPT and FHH patients, particularly between 0.01-0.02

If >2% almost certainly PHPT

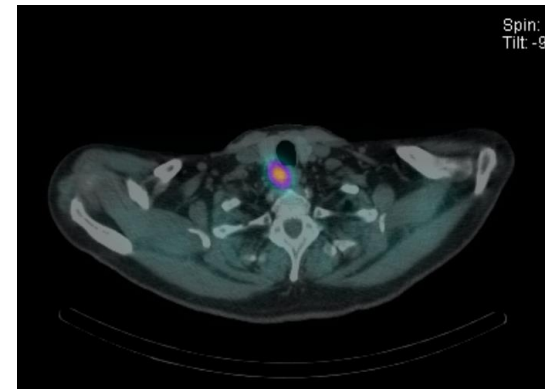
If <1% almost certainly FHH

1-2% not clear ?send for genetics

Think about screening family's Ca levels

# Surgery for PHPT

- Localise and excise
  - USS, sestaMIBI
  - Surgical exploration or selective adenectomy
  - Complications (uncommon)
    - ↓PTH, rec laryngeal nerve palsy
- **AVOID SURGERY IN FHH**



# Surgery vs conservative treatment

- Consider surgery if:
  - Wishes to have surgery
  - Symptomatic
  - Has low bone mineral density, kidney stones
- Conservative Rx
  - Bisphosphonates
  - Cinacalcet (calcimimetic, binds CaSR and suppresses PTH secretion)



# In this case...

- Admitted as Ca was  $>3.0$  and vomiting
- Given saline to lower Ca
- Elevated PTH 7.6 pmol/L, CCCR 2.3%
  - Therefore PHPT

➤ What next?

# PHPT in pregnancy

- Uncommon
- Effects on pregnancy
  - Nephrolithiasis, pancreatitis
  - Hyperemesis gravidarum
  - Pre-eclampsia (25%)
- Fetal effects
  - Fetal IUGR, low birth weight
  - Pre-term delivery
  - Postpartum neonatal hypoCa

# Dealing with PHPT in pregnancy

- Refer to experienced Obstetric Medicine centre
- Ultrasound localisation of PT adenomas
  - Sometimes MRI in 2<sup>nd</sup> trimester
  - sestaMIBI, CT etc involves radiation...
- IV fluids/antiemetics if hyperemetic
- Surgery in 2<sup>nd</sup> trimester
  - Patient and baby weathered well
  - Safe delivery
- MEN-1 screening required

# Case 2

- 55 year old man
- Tired
- Corrected Ca 2.34
- PTH 7.6 pmol/L (upper limit normal 6.4)

➤ What do you need to do?

# Secondary hyperparathyroidism

- Normal Ca, elevated PTH
- Vitamin D deficiency
- Chronic kidney disease
- Familial hypocalciuric hypercalcaemia
  - Does not always present with hypercalcaemia
- Mild primary hyperparathyroidism

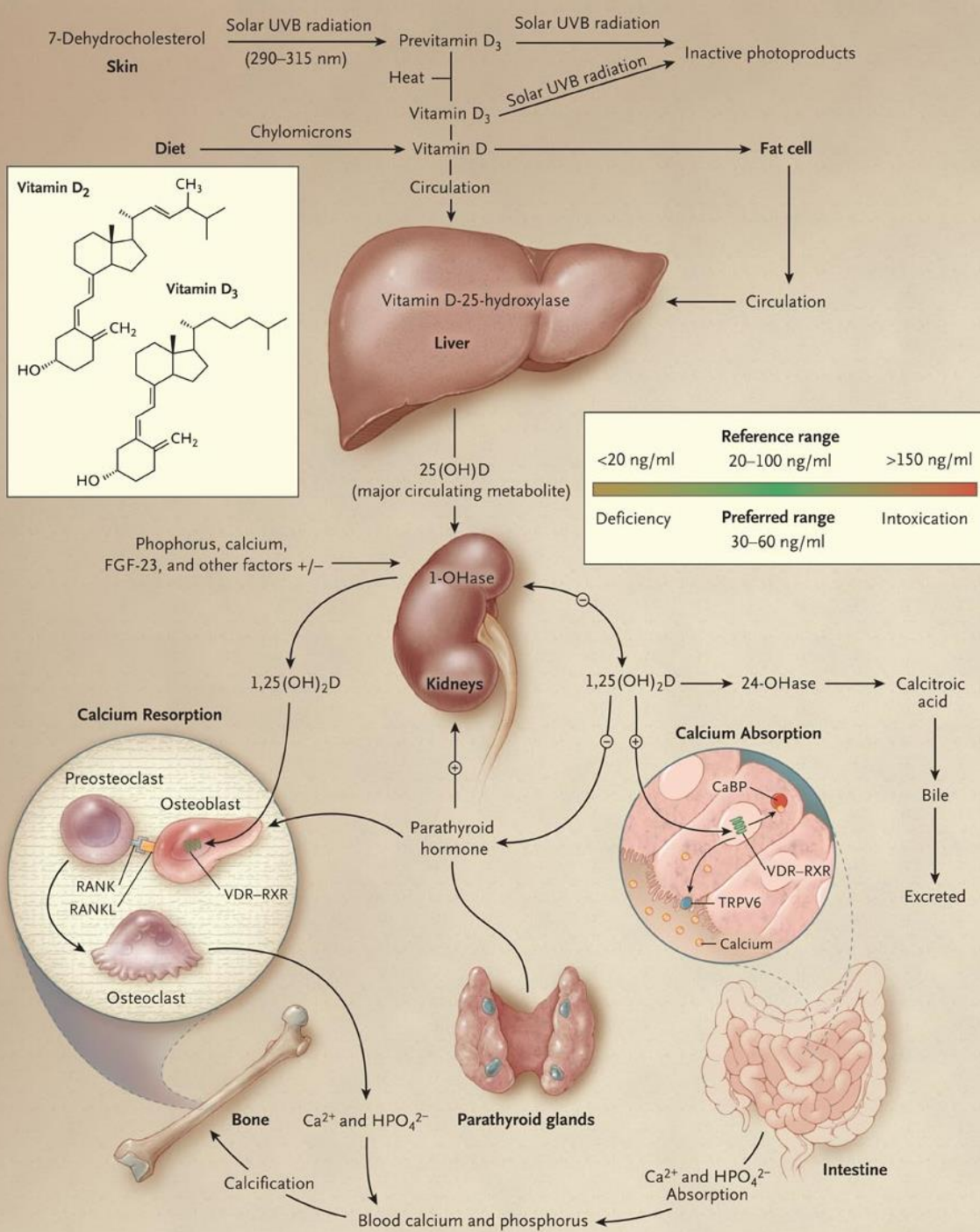
# Further tests

- Cr 65  $\mu\text{mol/L}$
- Vitamin D 15 nmol/L
  - Deficient <25 nmol/L
  - Insufficient 25-75 nmol/L
  - Sufficient >75 nmol/L

# Vit D Deficiency

- Children
  - Growth retardation in utero
  - Rickets – #, pseudo#, leg bowing
  - Short for age
- Adults
  - Secondary hyperparathyroidism
  - Low BMD → osteopenia/osteoporosis
  - Osteomalacia: muscle pain and weakness
  - Increased risk of fracture and falls





# Metabolism of Vitamin D



# Groups at risk for deficiency

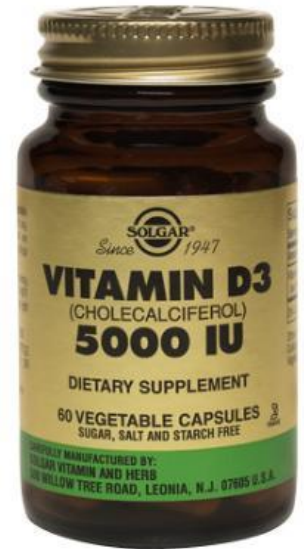
Mechanism	Examples
Reduced exposure to UV	High latitude, sunblock, clothing, institutionalization
Reduced skin synthesis	Melanin pigmentation, aging
Malabsorption	Pancreatic insufficiency, IBD, coeliac disease, bariatric surgery, cholestyramine, orlistat
Sequestration in fat	Obesity
Increased metabolism to calcitroic acid	Rifampicin, Phenytoin, Glucocorticoids, HAART, transplant drugs
Failure to 25-hydroxylate	Severe liver failure
Failure to 1-hydroxylate	CKD and hyperphosphataemia
Loss of Vitamin D in urine	Nephrotic syndrome

# When should I check vitamin D?

- Hyperparathyroidism
- Bone disease
  - osteomalacia, osteoporosis, or Paget's disease
- If having treatment where treating vitamin D deficiency is appropriate
  - Anti-resorptives, steroids
- If the person has had a fall
- Features of hypocalcaemia
  - muscle cramps, carpopedal spasm, numbness, paraesthesias, tetany, or seizure

# Supplements available

- Colecalciferol (D3)
  - Calcium + D3 2 tablets = 400–800 IU
  - 20,000 IU caps (pharmacy)
  - OTC: 400–5000 IU tabs, caps
- Ergocalciferol (D2)
  - IM 300,000–600,000 IU
  - Every 3-6 months



Note D3 >> D2 in potency in terms of ↑25OHD

# If vitamin D deficient... (<25 nmol/L)

- **Load** over 3 months
  - PO D3 (e.g. Dekristol) **20,000** IU weekly
  - IM D2 **300,000** IU 2x injections in 3 months
- Then go on to **maintenance**
  - **1000-2000** IU daily
  - Higher doses considered if accelerated metabolism or obesity
- **Check 25OHD, Ca** after 3 months
  - Then 6-monthly

## If Vitamin D insufficient... (25-75 nmol/L)

- Consider treatment if
  - Osteoporotic/penic or taking anti-resorptive
  - Symptomatic (widespread muscle pain etc)
  - High risk of deficiency
  - Malabsorption
  - Chronic disease (e.g. CKD)
- Tiredness is not a indication
- **Maintenance** dose: 1000-2000 IU daily

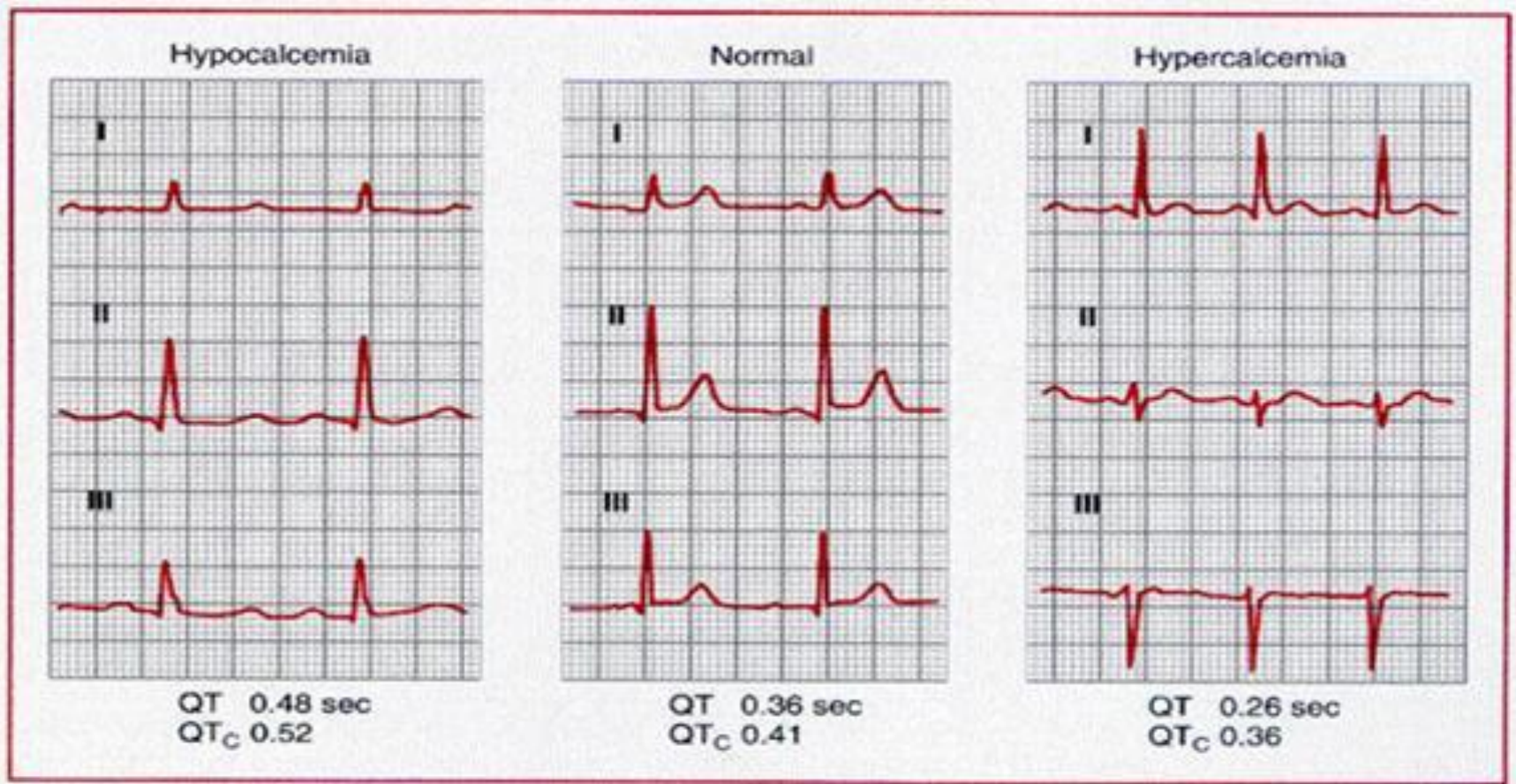
# Case 3

- 27 year old man post thyroidectomy
- Corrected Ca 1.72 mmol/L
- Ionised Ca 0.82 mmol/L

# Signs and Symptoms

- Asymptomatic
- Musculoskeletal
  - Cramps, paraesthesiae ... tetany, laryngospasm, respiratory depression
  - Chvostek's and Trousseau's signs
- CNS
  - Depression ... seizures, coma
- Cardiovascular
  - Prolonged QTc ... VF, VT ... pulseless electrical activity or asystole
  - Cardiac failure

# ECG changes





# Emergency guide

- Clinical assessment and ECG
- Check amylase, CK, U&E
- Ionised Ca measurement (if Alb ↓)
  
- If mild Sx and corrected Ca  $\geq 2.0$ 
  - Oral [Sandocal-1000](#) 1 tab bd
- If severe Sx and corrected Ca  $< 2.0$  or ECG changes
  - Admission required for IV Ca infusion
- Persistent ↓Ca  $> 48$ h
  - [Sandocal-1000](#) 1 tab bd plus [Alfacalcidol](#) 1  $\mu$ g od.

# Causes overview

↓PTH	PTH resistance	Vit D problems	Ca sequestration
No parathyroids (surgery, autoimmune)	Renal failure	Vit D deficiency	Pancreatitis
Mg deficiency	PseudohypoPTHism	Vit D dep rickets T1 (CYP27B1 defic)	Chelating/ppting agents (EDTA, PO <sub>4</sub> <sup>-</sup> )
PTH gene mutations		Vit D dep rickets T2 (VDR mutation)	Bisphosphonates
CaSR gain-of-function			Tumour lysis
			Rhabomyolysis
↓Ca ↑PO <sub>4</sub> ↓PTH	↓Ca ↑PO <sub>4</sub> ↑PTH	↓Ca ↓PO <sub>4</sub> ↑PTH	↓Ca ↑PO <sub>4</sub> ↑PTH

# Hypoparathyroidism

- Iatrogenic
  - Surgery to neck
  - Radiation therapy
- Autoimmune hypoparathyroidism
  - Reported also with immunotherapies for cancer
- Genetic causes
  - PTH mutations
  - Gain-of-function of Ca sensing receptor
  - As part of other syndromes (e.g. Di George syndrome)

# Treatment of hypoparathyroidism

- Standard treatment involves
  - Activated vitamin D (alfacalcidol or calcitriol)
  - Ca tablets
- Associated with elevated Ca excretion in urine
  - 31% of patients have renal calcification
  - Higher risk of acquiring CKD
- Target low-normal Ca levels
  - 2.10-2.30 mmol/L
  - Reduce Ca consumption as low as tolerated

# Treatment of hypoparathyroidism

- Recombinant PTH (1-84) – Natpara



- Approved in the US, not yet in Europe
- Corrects hypocalcaemia
  - Hypercalciuria still present, so this is still a problem
- Theoretical risk of osteosarcoma
  - Will require monitoring if approved

# Summary

- ↑Ca
  - If <3.0 can investigate as outpatient
  - 24h urine collection important to distinguish causes
- ↓Ca
  - ECG important
  - Replace with active vitamin D + Ca
- Vitamin D
  - Only needs to be checked and replaced in certain situations