Metabolic Bone Disease

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Hypercalcaemia

- Hyperparathyroidism
- Familial hypocalciuric hypercalcaemia
- Humoral hypercalcaemia of malignancy
- Local osteolytic hypercalcaemia

Hypocalcaemia

- Hypoparathyoidism
- Pseudohypoparathyroidism
- Vitamin D deficiency

Hypo and Hyperphosphataemia

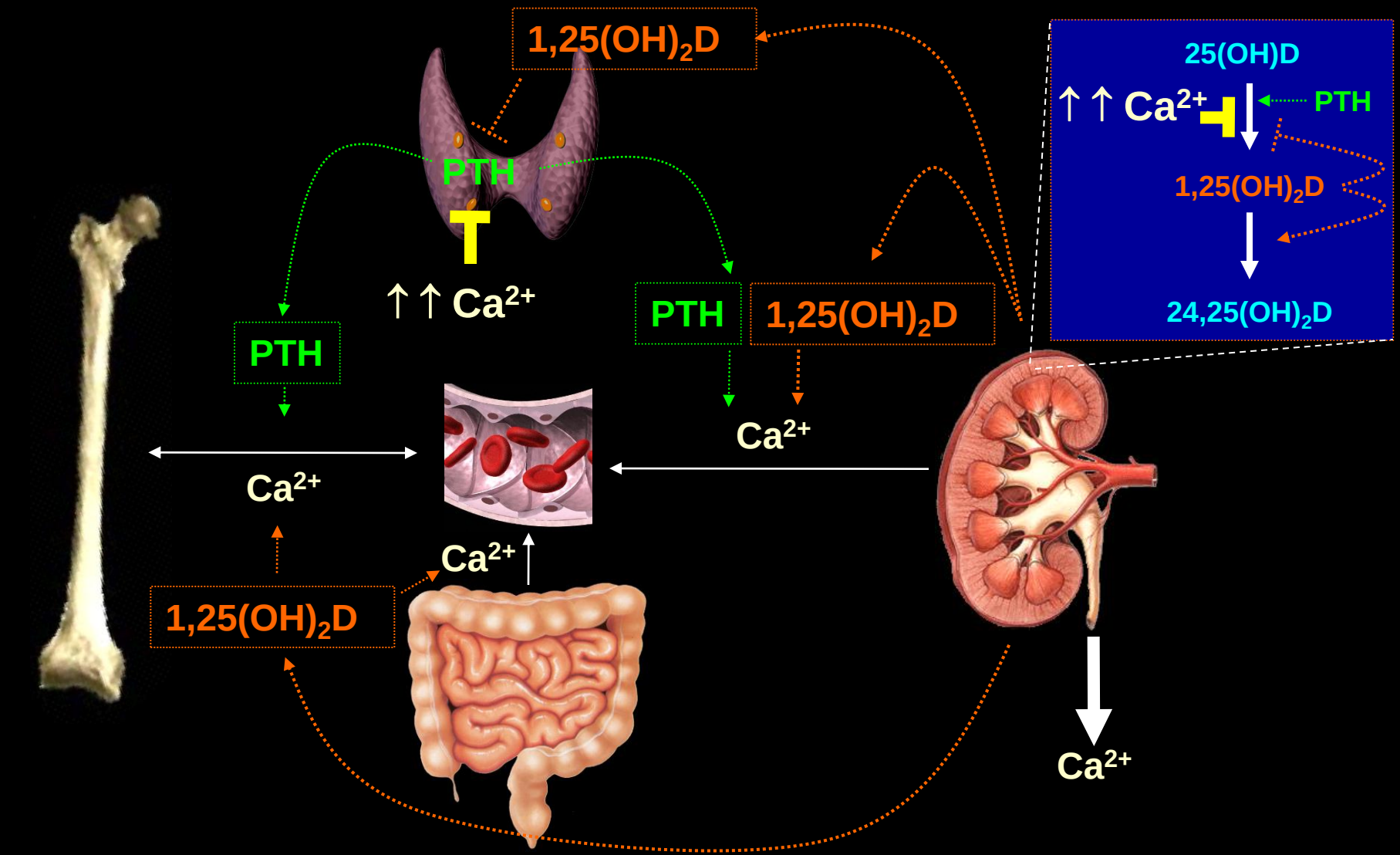
- X-linked hypophosphatemic rickets
- Chronic kidney disease - mineral bone disorder

Hypercalcaemia

Hypercalcaemia

- Clinical features
  - Most frequently asymptomatic
  - Renal
    - Polyuria/polydipsia, nephrocalcinosis/nephrolithiasis, renal failure
  - Central CNS
    - Lethargy, fatigue and depression
    - Ataxia, psychosis confusion and coma
  - Gastrointestinal
    - Dyspepsia/peptic ulceration, vomiting, constipation, pancreatitis
  - Musculoskeletal
    - Proxymal myopathy, hypotonia
  - Cardiovascular
    - Hypertension, bradycardia, short QT
- Mechanisms
  - Increased skeletal resorption (almost always involved)
  - Decreased renal excretion
  - Increased intestinal absorption

Physiological response to high calcium



High calcium suppresses PTH and inhibits 1α-hydroxylase activity

Low PTH/1,25(OH)$_2$D decreases renal resorption, skeletal resorption and Intestinal absorption

Differential diagnosis of hypercalcaemia

Parathyroid disorders (common in outpatients)

Primary hyperparathyroidism (Incidence 1:1000, 20/100,000 cases per year)

- **Autonomous PTH synthesis and release**
  - **80% single parathyroid adenoma,**
  - **15% multi glandular hyperplasia**
- **Rare familial forms**
  - **MEN1 (Menin): Parathyroid, Pituitary and Pancreatic islet cell**
  - **FIHPT (Menin): Parathyroid**
  - **MEN2 (Ret): Medullary thyroid carcinoma, Parathyroid and Phaeochromocytoma**
  - **HPT-JT (Hrpt2): Parathyroid adenoma and carcinoma, jaw fibromas Wilms tumour and uterine tumours**

Familial hypocalciuric hypercalcaemia (FHH)

- **Loss of function mutations of calcium sensing receptor (CaSR)**
  - **Alters calcium set point in parathyroid and kidney**

Differential diagnosis of hypercalcaemia

- Malignancy related (common in hospital inpatients)
  - Humoral hypercalcaemia of malignancy (HHM)
    - PTHrP secretion by tumour
    - Excess $1,25(OH)_2D$ from lymphoma
    - Ectopic PTH (very rare)
  - Local osteolytic hypercalcaemia (LOH)
    - Widespread local bone resorption
    - (myeloma, lymphoma or leukemia deposits)

- Other causes
  - Granulomatous diseases
    - Macrophage synthesis of $1,25(OH)_2D$
    - (TB, sarcoid, inflammatory bowel disease)
  - Endocrine diseases
    - Thyrotoxicosis, Addison's and Phaeochromocytoma
  - Iatrogenic
    - 25-OHD intoxication, Thiazides, Lithium

Investigations

Corrected Ca^{2+}	2.1-2.60mmol/l
PO_4^{3-}	0.8-1.4mmol/l
Mg^{2+}	0.7-1.00mmol/l
Alkaline phosphatase	30-130 IU/L
Creatinine	60-110μmol/l
PTH	1.1-6.8pmol/l
25-OHD	25-120nmol/l
Urinary Ca^{2+}	0-7.5mmol/24h

Calcium is bound to serum proteins

Corrected calcium = Total serum calcium + 0.1 x ((40 - serum albumin)/4)

Primary hyperparathyroidism

Aetiology (Parathyroid adenoma or hyperplasia)

- 80% single parathyroid adenoma,
- 15% multi glandular hyperplasia

Biochemistry

- ↑Ca^{2+}, ↓PO_4^{3-}, ↑ALP, ↑PTH
- ~~Calcium/creatinine clearance ratio >0.01~~ (Cre in mmol/l !!)
- (Urinary Ca^{2+} x Serum Creatinine)
- (Serum Ca^{2+} x Urinary Creatinine)

Imaging

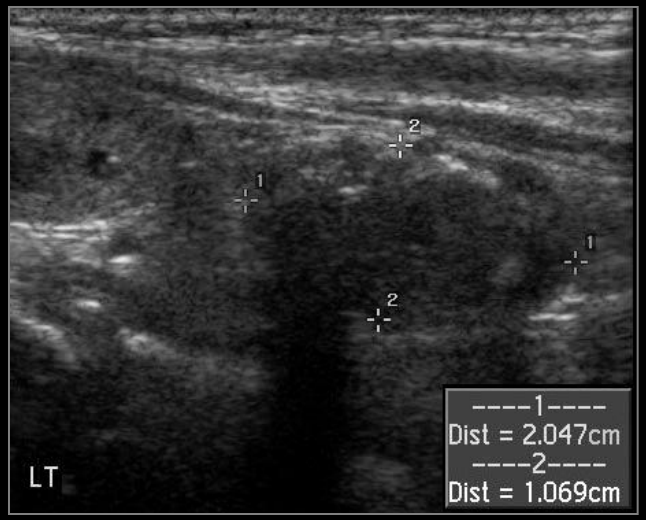
- Renal Ultrasound (Nephrolithiasis, Nephrocalcinosis)
- DXA scan (Decreased bone mineral density)

Localisation of parathyroid adenoma

- Neck Ultrasound
- Parathyroid scan (Technecium-99 Sestamibi with SPECT)

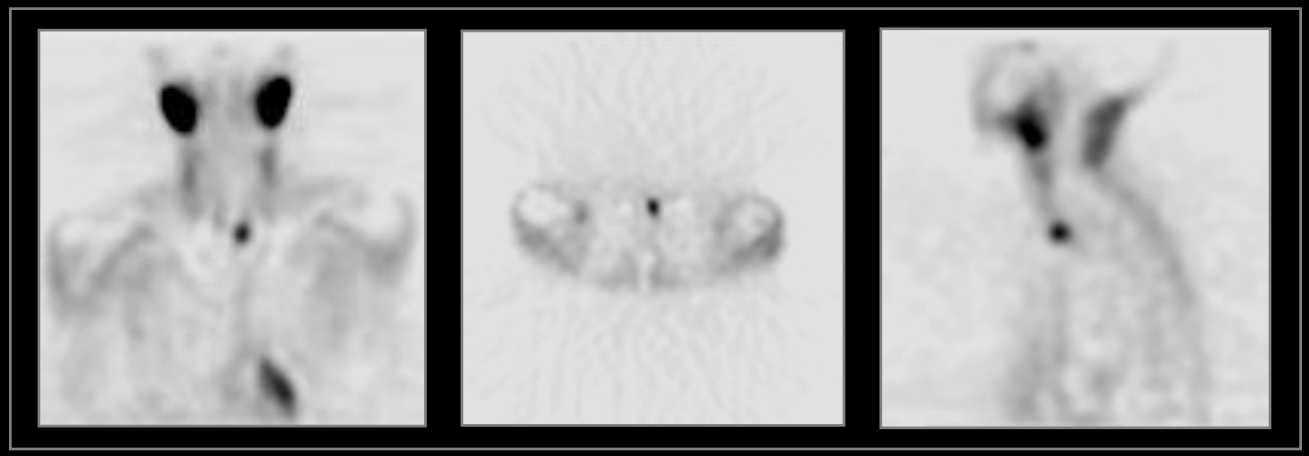
Parathyroid localisation

Neck Ultrasound



Left inferior 2.0x1.0cm parathyroid adenoma

Tc99 MIBI with SPECT



left Inferior parathyroid adenoma

Treatment of 1^0HPT

Indications for treatment of asymtomatic 1^0HPT

Ca^{2+}	>2.85mml/l (vitamin D deficiency)
(uCa	>10mmol/d?)
Creatinine clearance	<60ml/min
BMD	T score <-2.5 or fracture
Age	<50y

Treatment

- Open or minimally invasive parathyroidectomy
- Complications of surgery (1%)
  - Hypoparathyroidism
  - Recurrent laryngeal nerve palsy

Patients who are not candidates for surgery

- Medical follow up and high fluid intake (usually stable)
- Bisphosphonates (reduce osteoclastic bone resorption)
- Cinacalcet CaSR (calcimimetic) (reduce PTH secretion)

(3rd international workshop on PHPT (2009) J Clin Endocrinol Metab. 94:333-381)

Familial hypocalciuric hypercalcaemia

Familial hypocalciuric hypercalcaemia (FHH)

- Autosomal dominant (2% hypercalcaemia)
- Heterozygous loss of function mutations of *CASR*
- Increase in parathyroid gland calcium set-point
- Mild enlargement of parathyroids

Presentation

- Asymptomatic
- Life long moderate ↑Ca^{2+} ,
  →↓PO_4^{3-}, ↑→Mg^{+}, →ALP, ↑→PTH
- Calcium/creatinine clearance ratio <0.01
- Check Ca^{2+} in family members

Management

- Compatible with normal life in almost all cases
- *CASR* mutational analysis rarely required
- SURGERY is NOT REQUIRED !

Humoral hypercalcaemia of malignancy

Aetiology of HHM

- 80% are due to PTHrP secretion by HHM associated tumour
- Lung, oesophagus, breast, renal and cervical most common

Presentation

- Rapid onset severe symptoms of hypercalcaemia
- Frequently life threatening Ca^{2+} (>4mmol/l)
- Identify tumour by clinical examination?

Investigations

- ↑↑ Ca^{2+}, ↓PO_4^{3-}, ↑ALP, undetectable PTH, ↑PTHrP

Imaging

- CT scanning to identify tumour
- Bone scan to identify skeletal metastasis

Management

- Increase Ca^{2+} clearance with IV fluids and loop diuretics
- Reduce osteoclastic resorption with iv bisphosphonates
- Identify and remove tumour but very poor prognosis

Hypocalcaemia

Hypocalcaemia

Clinical features

- May be asymptomatic especially if mild or of gradual onset
- Musculoskeletal
  - Fatigue, cramps, paresthesia, tetany, stridor and laryngospasm
  - Carpopedal spasm, Chvosteck's and Trousseau's signs
- CNS (Basal ganglia calcification and subcapsular cataracts)
  - Twitching and generalised seizures
  - Mental retardation, depression, coma
- Cardiovascular
  - Prolongued QT interval
  - Congestive cardiac failure

Mechanism

- PTH deficiency or PTH resistance (rare)
- Vitamin D deficiency or Vitamin D resistance (very rare)

Investigation

- Ca^{2+}, PO_4^{3-}, Alk Phos, Mg^{2+}, Cre, PTH and 25OHD
  - (Thyroid function, LH/FSH, E2, testosterone)
  - (Skull and hand radiographs)

Hypoparathyroidism

(PTH deficiency)

Hypoparathyroidism

↓Ca^{2+}, ↑PO_4^{3-}, ↓ or undetectable PTH

Aetiology

- **Surgical removal or parathyroid irradiation**
- **Autoimmune destruction (APECED)**
- **Failure of parathyroid developmental (DiGeorge syndrome)**
- **Magnesium deficiency (Impaired PTH synthesis and release)**
- **Rare familial conditions (PTH mutations, *CASR* activating mutations)**

Hypoparathyroidism

(PTH deficiency)

Acute treatment

- Tetany requires IV calcium gluconate, careful observation for stridor
- Oral calcium and 1α-OHD (Increases intestinal calcium absorption)
- (Not 25-OHD since PTH required for 1α-hydroxylation)

Chronic treatment

- Oral calcium and 1α-OHD
- Ca^{2+} should be maintained at the lower limit of normal 2.0mmol/l
  - (Without PTH's hypocalciuric effect risk of renal calcification)
  - (Intermittent PTH injections are also beginning to be used)

Lifelong follow up is required

Pseudohypoparathyroidism

(Renal PTH resistance)

Pseudohypoparathyroidism

- Heterozygous mutations effecting *GNAS* locus
- Encodes Gαs protein involved in G-protein coupled receptor signalling
  - (PTH, TSH, FSH/LH, GHrH, Glucagon etc)
- Both *GNAS* alleles are expressed in most tissues
- Only maternal allele is imprinted and expressed in proximal renal tubule

Actions of PTH in PCT are mediated by Gαs

- If maternal *GNAS* allele is mutated no functional Gαs is expressed in PCT
  - Renal PTH resistance impaired Ca^{2+} resorption and PO_4^{3-} excretion

Normal skeletal and neural development requires 2 functional *GNAS* alleles

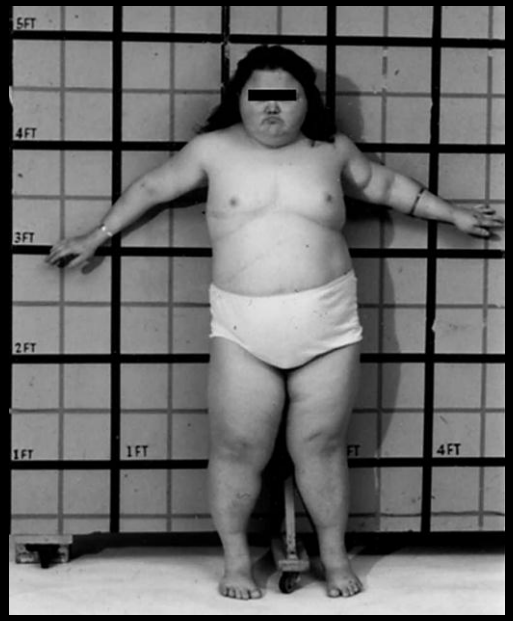
- Mutation of either *GNAS* allele: Albrights Hereditary Osteodystrophy

With time TSH, FSH/LH and GHrH signalling may also be impaired

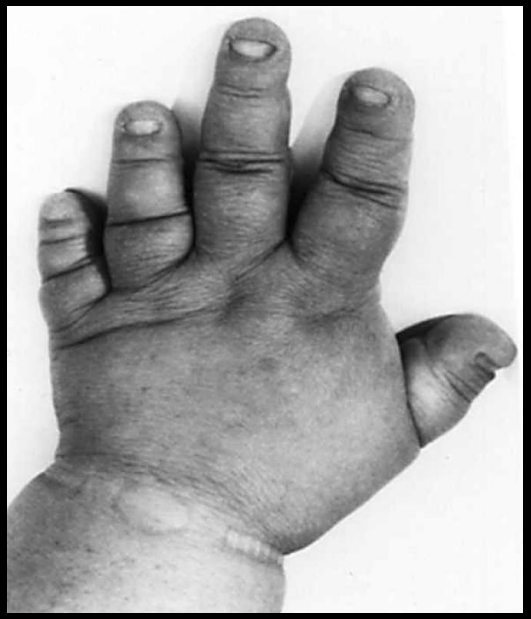
- Primary hypothyroidism, hypogonadism and GH deficiency

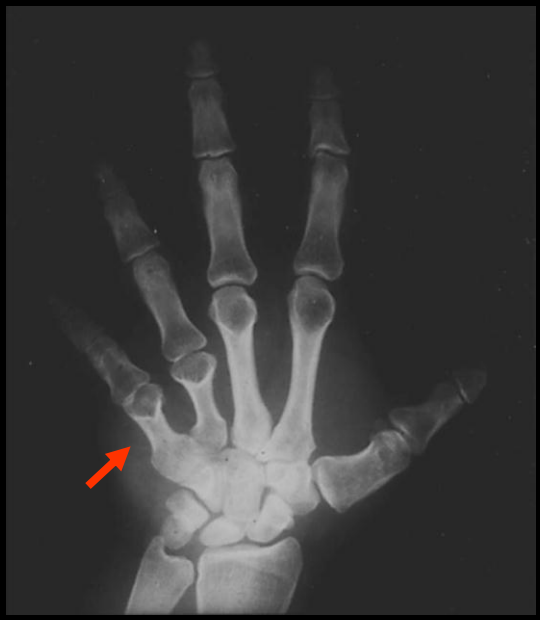
(Mantovani G (2006) Best Pract Res Clin Endocrinol Metab.20:501-13)

Albright Hereditary Osteodystrophy
AHO



Short, obese, round face
Mild mental retardation





Brachydactyly with short 4th and 5th metacarpals and metatarsals
Subcutaneous ossification

Vitamin D Deficiency

Current guidance on vitamin D

Dietary intake and synthesised by skin

- Average dietary intake 200 IU/d
- Minimal erythemal dose of sunlight ≡ 25,000 IU ergocalciferol
  - In UK for 6 months there is no appropriate UV light (290-315nM)

Dietary sources

- Eggs, Butter and Oily fish (salmon, herring, mackerel and tuna)

Current Government guidelines for daily requirement

<50y	200IU/d
50-70	400IU/d
>70	600IU/d (Elderly make 70% less in skin)

Risk factors for deficiency

- Ethnic origin South Asian and Afro-Caribbean
- Diet (elderly, care home residents, vegan)
- UV exposure (northern latitudes, pigmented skin, dress, sun screens)

400IU/d supplements recommended for

- Infants, pregnant and lactating women, at risk ethnic groups and >65y

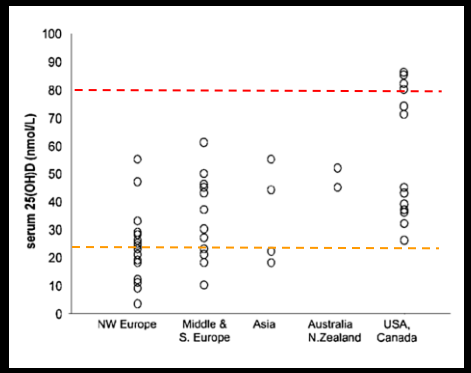
Maximum recommended daily dose 2000 IU

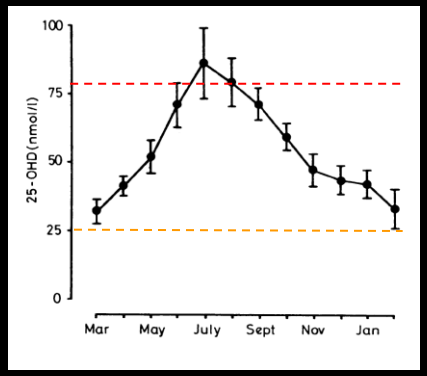
Vitamin D supplementation is the most commonly used medication in the world and is worth $1000 million per annum

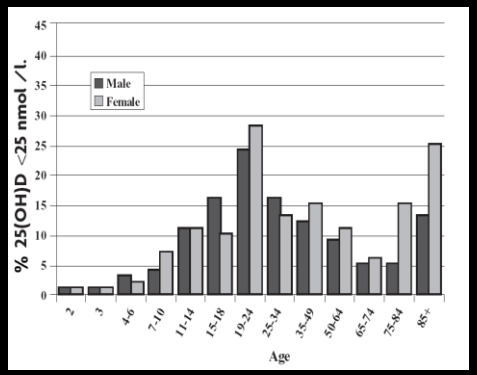
(Vieth R 2007 Am J Clin Nutr 85:649)

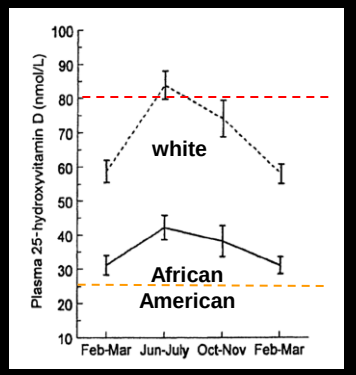
Vitamin D normal range?

Pro-hormone 25-OHD levels are an indicator of vitamin D status
But what should be the normal range for 25-OHD
Varies with latitude, season, age, ethnic origin and adiposity









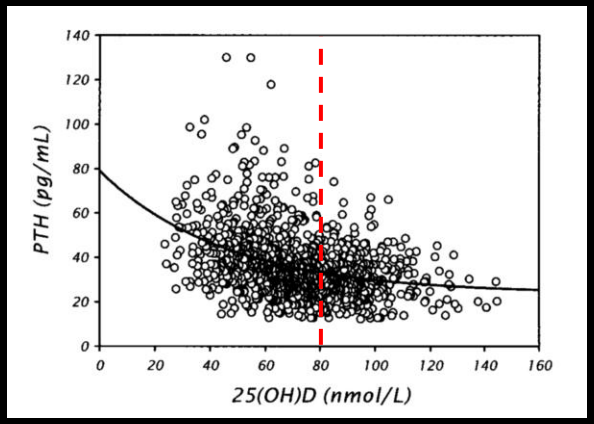
25-OHD$_3$ of <25nM have previously been considered suboptimal (DoH 1998)
Many now suggest that 25-OHD$_3$ should be 40nM or even >75-80nM

Vitamin D deficiency	**<25nM**
Vitamin D insufficiency	**25-80nM**
Vitamin D sufficiency	**80-200nM**
Vitamin D toxicity	**>200nM**

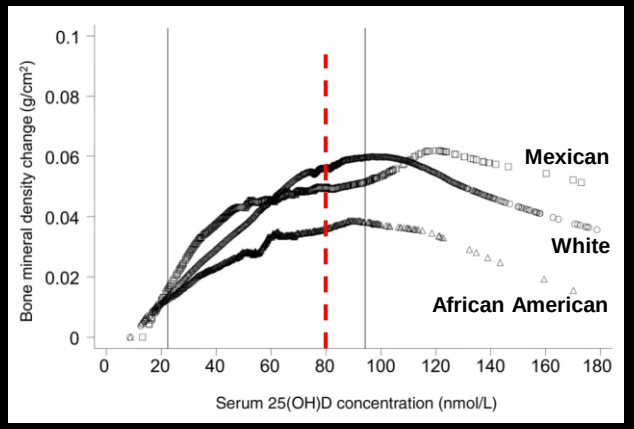
(Lips P 2001 Endo Rev 22:477-501; Juttmann JR et al 1981 BMJ 282:1349-1352; Jones G et al 2007 JBMR 22:v11-v15
Position statement by the Scientific Advisory Committee on Nutrition 2008)

Maintenance of vitamin D >80nM?

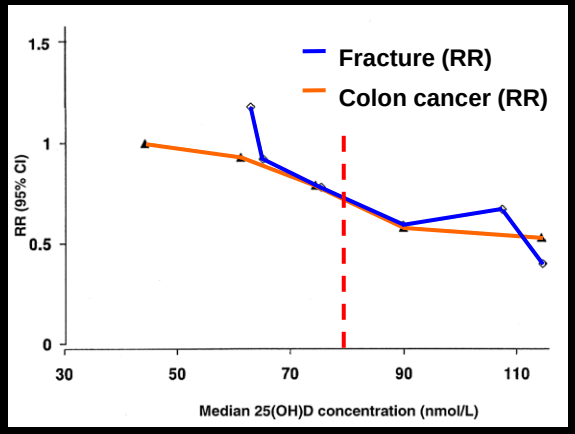
Maximum PTH suppression



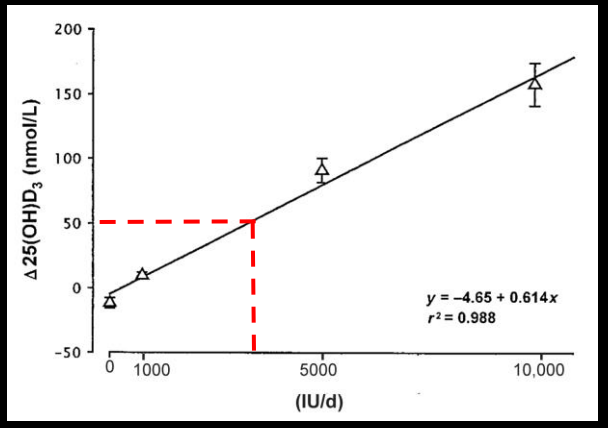
Peak BMD at 80-100mM



Reduces # and cancer risk



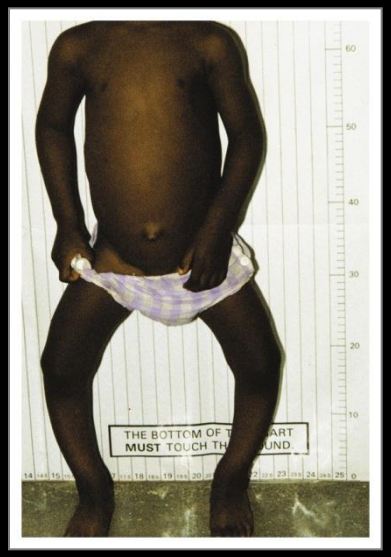
To maintain 25-OHD >80nM requires 3,000 - 4,000 IU/d

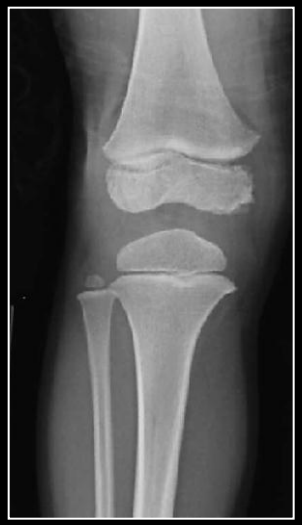


(Bischoff-Ferrari HA et al 2006 Am J Clin Nutr 84:18-28; Heaney RP 2003 Am J Clin Nutr 77:204-210)

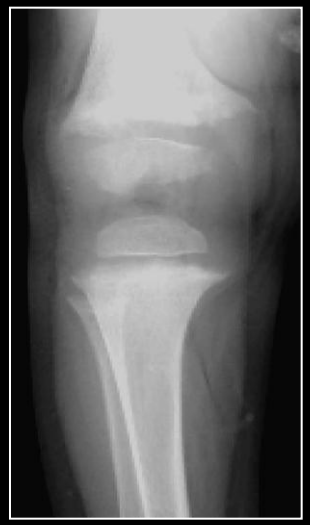
Vitamin D deficiency in chindhood

(low 25-OHD, low Ca^{2+}, low PO_4^{3-} and high PTH)





Normal



Rickets

Rickets
Hypocalcaemia and hypophosphataemia during growth

Growth plate
Apoptosis of growth plate chondrocytes requires phosphate (Caspase 9)
(Failure of apoptosis results in gross disorganisation of the growth plates impaired growth and deformity)

Cortical bone
Failure of mineralisation of newly formed osteoid due to low Ca^{2+} and PO_4^{3-}
(Bowing of long bones)

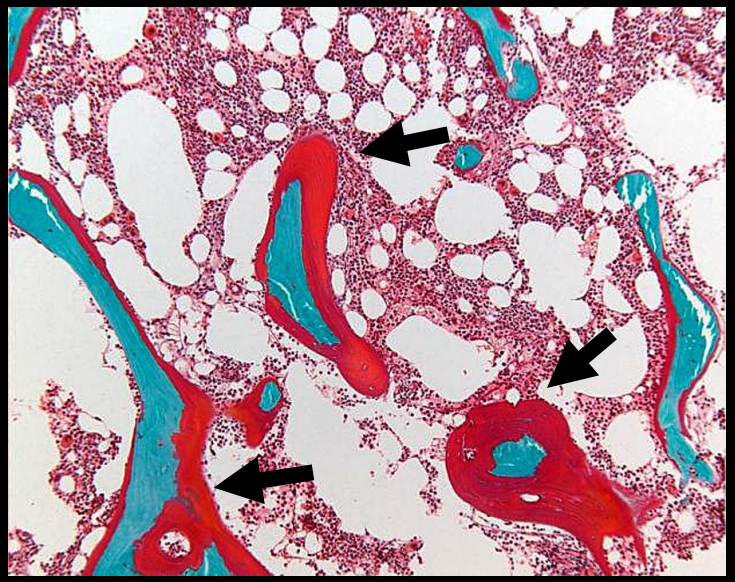
Rachitic rosary in ribs
Bone pain, muscle weakness, poor mobility
May have tetany and seizures

NEJM 2009 360(3)

Vitamin D deficiency in adults

(low 25-OHD, low Ca^{2+}, low PO_4^{3-} and high PTH)

Mineralised osteoid in green



non-mineralisation osteoid in red

Osteomalacia

May result in hypocalcaemic symptoms

- But often absent as inevitably chronic deficiency

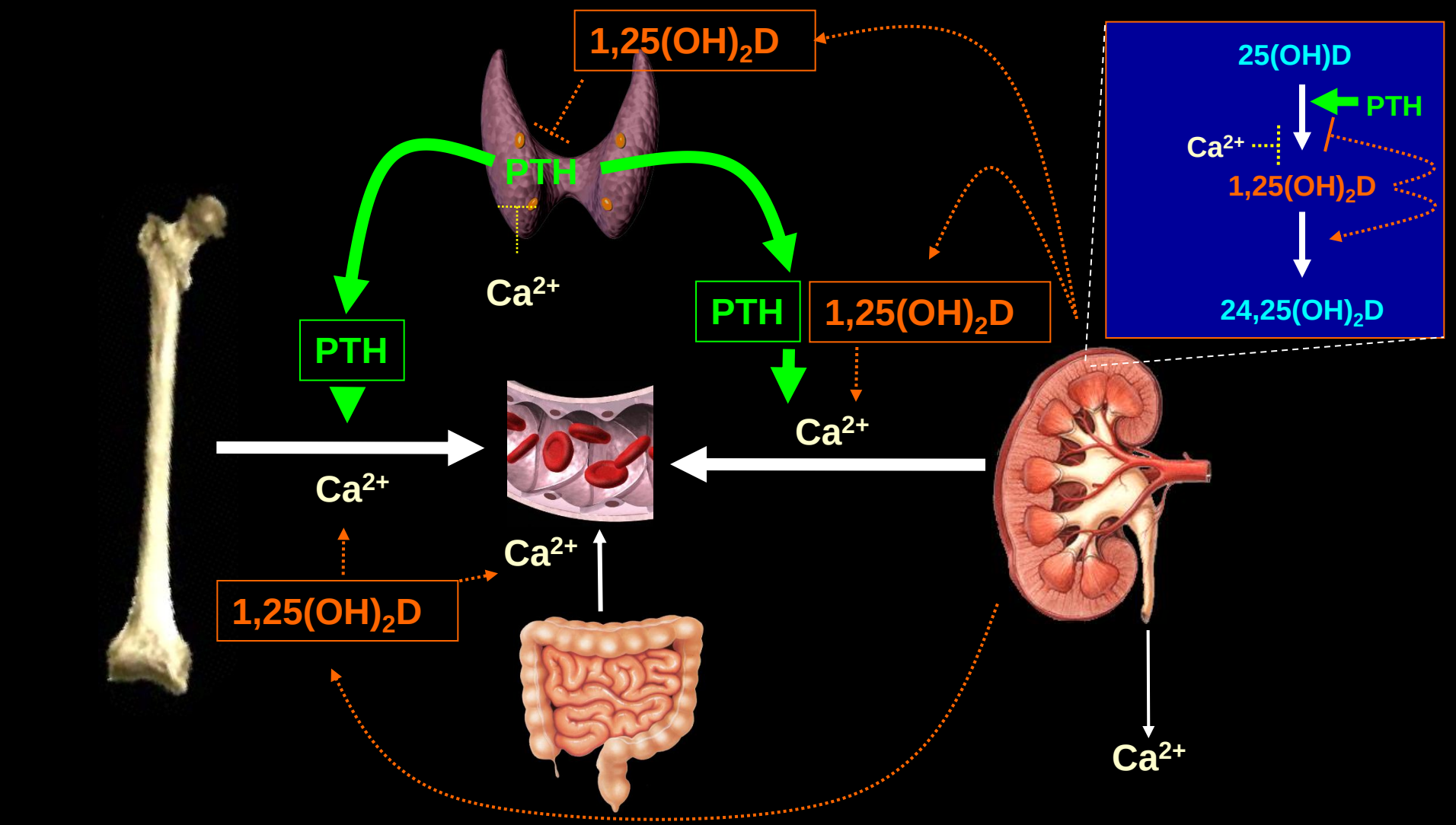
Bone pain, proximal muscle weakness

- Difficulty standing and walking

Reduced osteoid mineralisation

- Increased fracture risk

Vitamin D deficiency and calcium

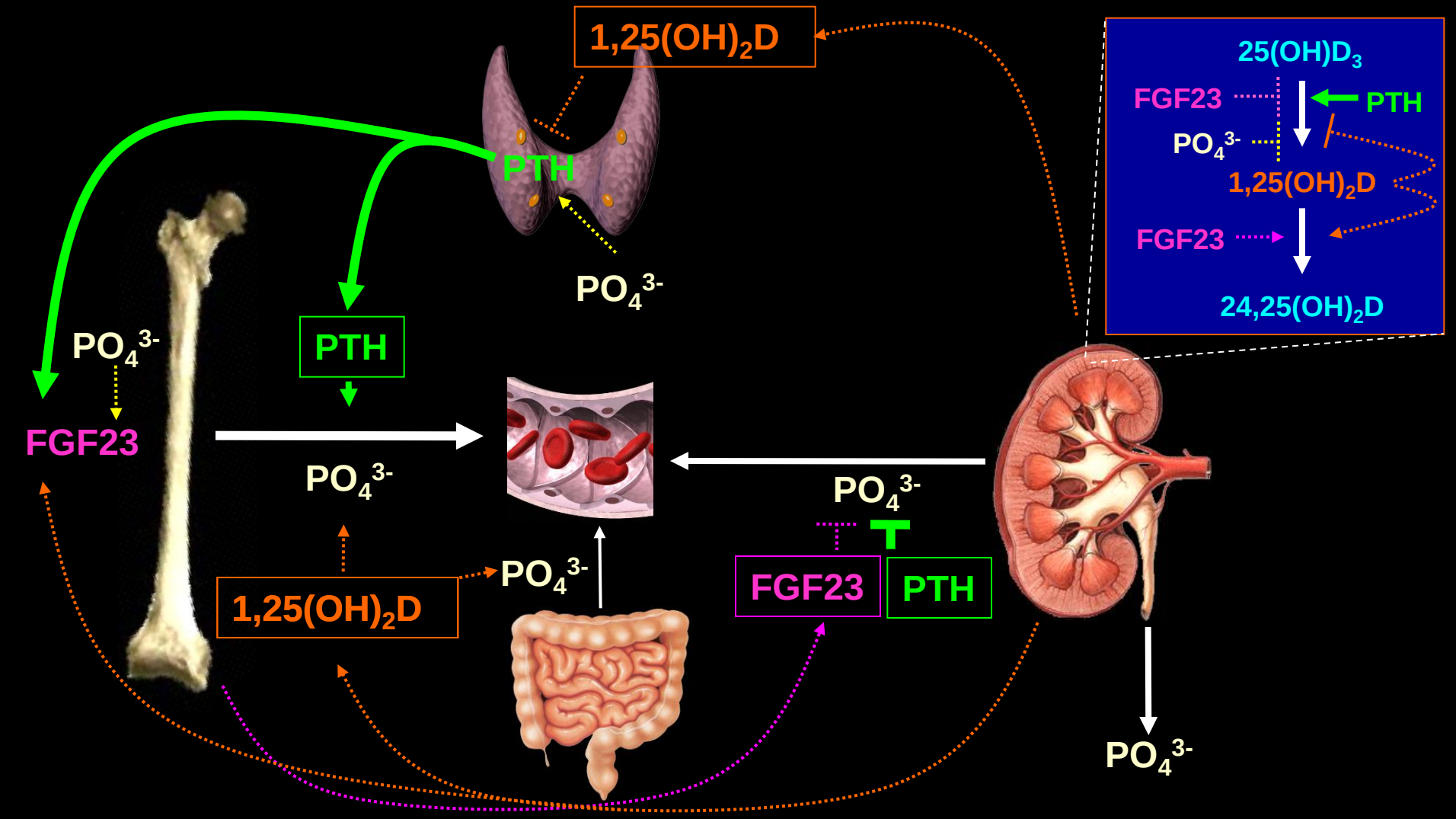


Low $1,25(OH)_2D$ reduces intestinal absorption of Ca^{2+}

Low Ca^{2+} and $1,25(OH)_2D$ increases PTH synthesis and secretion

High PTH increases Ca^{2+} resorption form bone and kidney and 1α-hydroxylase activity

Vitamin D deficiency and phosphate



Low $1,25(OH)_2D$ reduces intestinal absorption of PO_4^{3-}

Low $1,25(OH)_2D$ and PO_4^{3-} inhibits FGF23 synthesis increasing renal PO_4^{3-} resorption

High PTH increases PO_4^{3-} resorption form bone

High PTH, low FGF23 and low PO_4^{3-} all increase 1α-hydroxylase activity

Differential diagnosis of vitamin D deficiency

Nutritional
- Diet, UV exposure

Malabsorption
- Coeliac, Crohns, gastric/duodenal surgery, pancreatitis

Impaired vitamin D metabolism
- Liver disease (reduced 25-hydroxylase activity)
- Renal disease (reduced 1α-hydroxylase activity)

Increased metabolism
- Phenytoin and phenbarbital, rifampicin

Treatment
- Treatment dose until 25-OHD is >50nM
- Intra muscular injection 300,000 IU of 25-OHD_2 every 3 months
- Oral supplementation 40,000 IU 25-OHD_3 per week for 8 weeks

Vitamin D Resistance

(Very rare)

Vitamin D-dependent Rickets, Type I (Ligand deficiency)

- **Autosomal recessive: mutation of 1α-hydroxylase (CYP27B1)**
  - **Rickets, growth retardation**
  - **↓↓Ca^{2+}, ↓↓PO_4^{3-} , ↑PTH, ↑25-OHD and ↓↓$1,25(OH)_2D$**
- **Rx Physiological $1,25(OH)_2D_3$**
  - **High dose calcium also cures the rickets**

Vitamin D-dependent Rickets, Type II (Receptor deficiency)

- **Autosomal recessive: inactivating mutation of Vitamin D receptor**
  - **Rickets, growth retardation and alopecia**
  - **↓↓Ca^{2+}, ↓↓PO_4^{3-} , ↑PTH, →25-OHD and ↑$1,25(OH)_2D$**
- **Rx high dose calcium cures the rickets**

Hypophosphataemia

Hypophosphatemia

Hypophosphatemia

- ↓PO_4^{3-} is common especially in alcoholics and septic patients
- Severe in chronic alcoholics, refeeding syndrome, DKA and critical illness

Clinical features

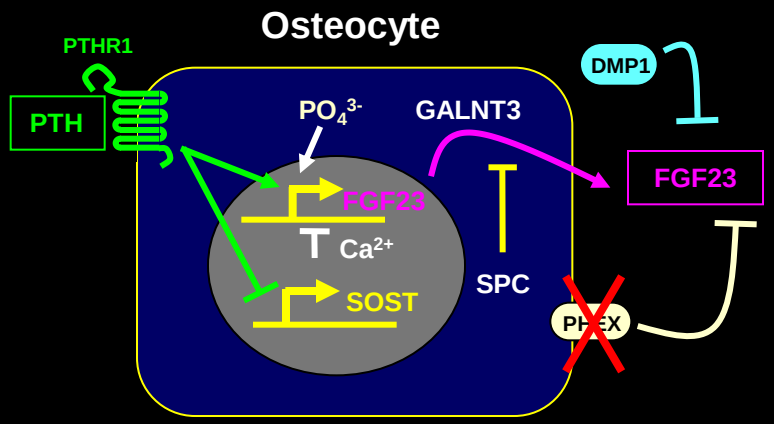
- Irritability, confusion seizures, coma
- Haemolysis and thrombocytopenia
- Muscle weakness, myopathy, rhabdomyolysis, cardiomyopathy
- Hypercalciuria and hypermagnesuria, glycosuria
- Impaired gluconeogenesis, Insulin resistance and hypoparathyroidism
- Metabolic acidosis

Mechanism (mild hypophosphatemia in vitamin D deficiency)

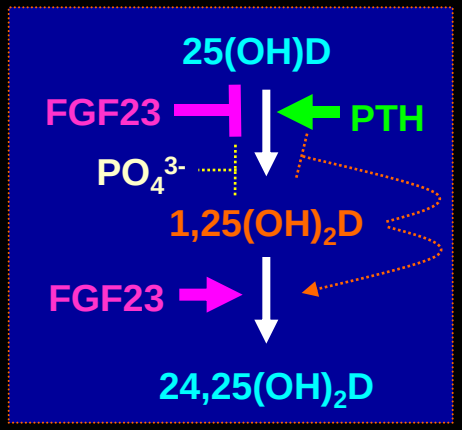
- Redistribution of PO_4^{3-} into cells
  - Increased synthesis of phosphorylated carbohydrates
- Increased renal excretion
  - ↑PTH, ↑FGF23, ↑KLOTHO
- Decreased intestinal absorption
  - Aluminium/magnesium antacids, chronic diarrhoea

X-linked hypophosphatemic rickets

Incidence 1:20,000



PHEX: metalloendopeptidase
negatively regulates FGF23 signalling



X-linked hypophosphatemic rickets (XLH) (Enhanced FGF23 signalling)

X-linked dominant: inactivating mutation of PHEX

Growth retardation, rickets and osteomalacia

Defective vitamin D metabolism and PO_4^{3-} resorption

$\rightarrow Ca^{2+}$, $\downarrow\downarrow PO_4^{3-}$, $\uparrow$PTH, $\downarrow 1,25(OH)_2D$

Rx $1,25(OH)_2D_3$ and phosphate supplements cures the rickets

Hyperphosphataemia

Hyperphosphataemia

Mechanism

- **Redistribution of PO_4^{3-} out of cells**
  - **Rhabdomyolysis, tumour lysis syndrome, trauma**

- **Decreased renal excretion**
  - **Renal failure**
  - **Hypoparathyroidism**
  - **Pseudohypoparathyroidism**
  - **Impaired FGF23 signalling**

- **Increased intestinal absorption**
  - **phosphate laxatives and enemas**

Phosphate homeostasis in CKD

Highest FGF23 levels are found in end stage CKD (100-1000x)

Early CKD (GFR<90): Nephron loss results in reduced filtered PO_4^{3-}

Increased FGF23 stimulates urinary PO_4^{3-} excretion

Reduced $1,25(OH)_2D$ increases PTH which stimulates PO_4^{3-} excretion

FGF23 compensation prevents hyperphosphataemia

End stage CKD: Failure of compensation

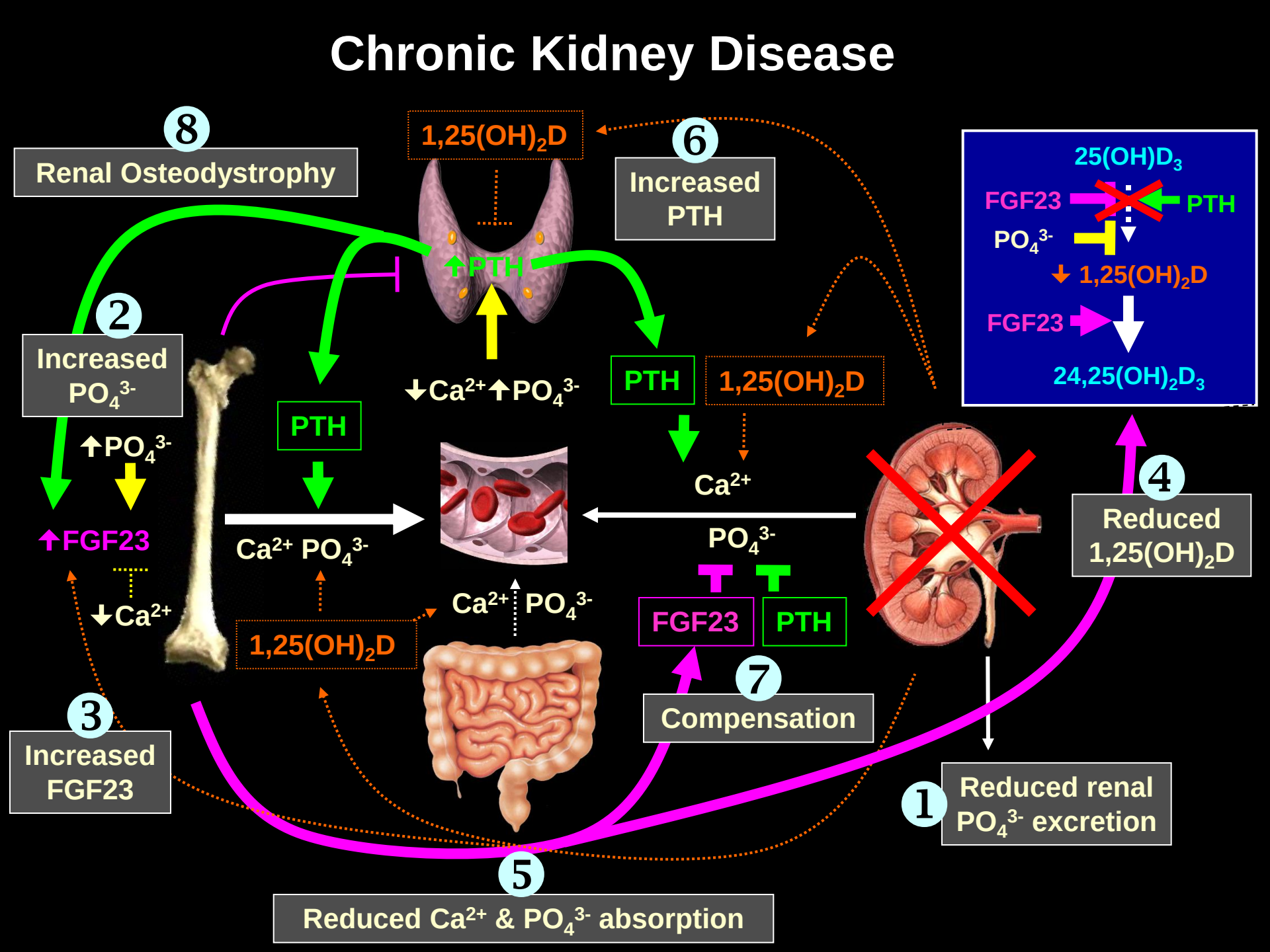
Hyperphosphataemia despite extremely high FGF23 levels

FGF23 levels correlate with

BMD, LVH, vascular calcification, CKD progression and mortality

(Juppner H et al 2010 J Bone Miner Res. 25:2091-7)

Chronic Kidney Disease



Prevention and treatment of CKD

Treat once ↑PO_4^{3-},↓$1,25(OH)_2D$
(CKD stage 3 Cre/Clearance <60ml/min/1.73m^2)

Oral phosphate binders
(reduce PO_4^{3-} absorption from gut)

Calcitriol ($1,25(OH)_2D_3$)
(reduces PTH and improves mineralisation)

References

General

Williams Textbook of Endocrinology 11th Edition (Editors Kronenberg HM, Melmed S, Polonsky KS and Larsen PR (Saunders)

Pseudohypoparathyroidism

Mantovani G (2006) Mutations in the Gs alpha gene causing hormone resistance. Best Pract Res Clin Endocrinol Metab.20:501-13

Vitamin D

Holick MF (2007) Vitamin D deficiency. N Engl J Med. 357:266-281

Bouillon R et al (2008) Vitamin D and human health: lessons from vitamin D receptor null mice. Endocr Rev. 29:726-76.

FGF23

Razzaque MS, Lanske B. (2007) The emerging role of the fibroblast growth factor-23-klotho axis in renal regulation of phosphate homeostasis. J Endocrinol. 194:1-10.

Learning objectives

1. Describe the common causes of hypocalcaemia.
2. Describe the signs and symptoms of hypocalcaemia
3. Describe the common causes of hypercalcaemia.
4. Describe the signs and symptoms of hypercalcaemia
5. Describe the investigation and management of 1^0HPT
6. Describe the causes of hypercalcaemia and undetectable PTH
7. Describe the signs and symptoms of vitamin D deficiency in children
8. Describe the signs and symptoms of vitamin D deficiency in adults
9. Describe the investigation and management of vitamin D deficiency
10. Describe how chronic renal failure effects FGF23, 1,25(OH)2D and PTH
11. Explain why $1,25(OH)_2D$ is used in treatment of chronic renal failure