Metabolic Bone Disease

Duncan Bassett
Molecular Endocrinology Group

Hypercalcaemia

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

Hypocalcaemia

- Hypoparathyoidism
- Pseudohypoparathyroidism
- Pseudo-pseudohypoparathyroidism
- Vitamin D deficiency

Hypo and Hyperphosphataemia

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

Calcium homeostasis

Calcium is essential for

- **Normal function of muscle, nerve, bone and coagulation**

Daily requirement

- **1000mg/d normal adult**
- **1300mg/d during growth, pregnancy and lactation,**
- **1200mg/d in the elderly**

Dietary sources

- **Milk, cheese other dairy products**
- **Dark leafy greens or dried beans**

Calcium concentration is very tightly regulated (2.1-2.6 mmol/l)

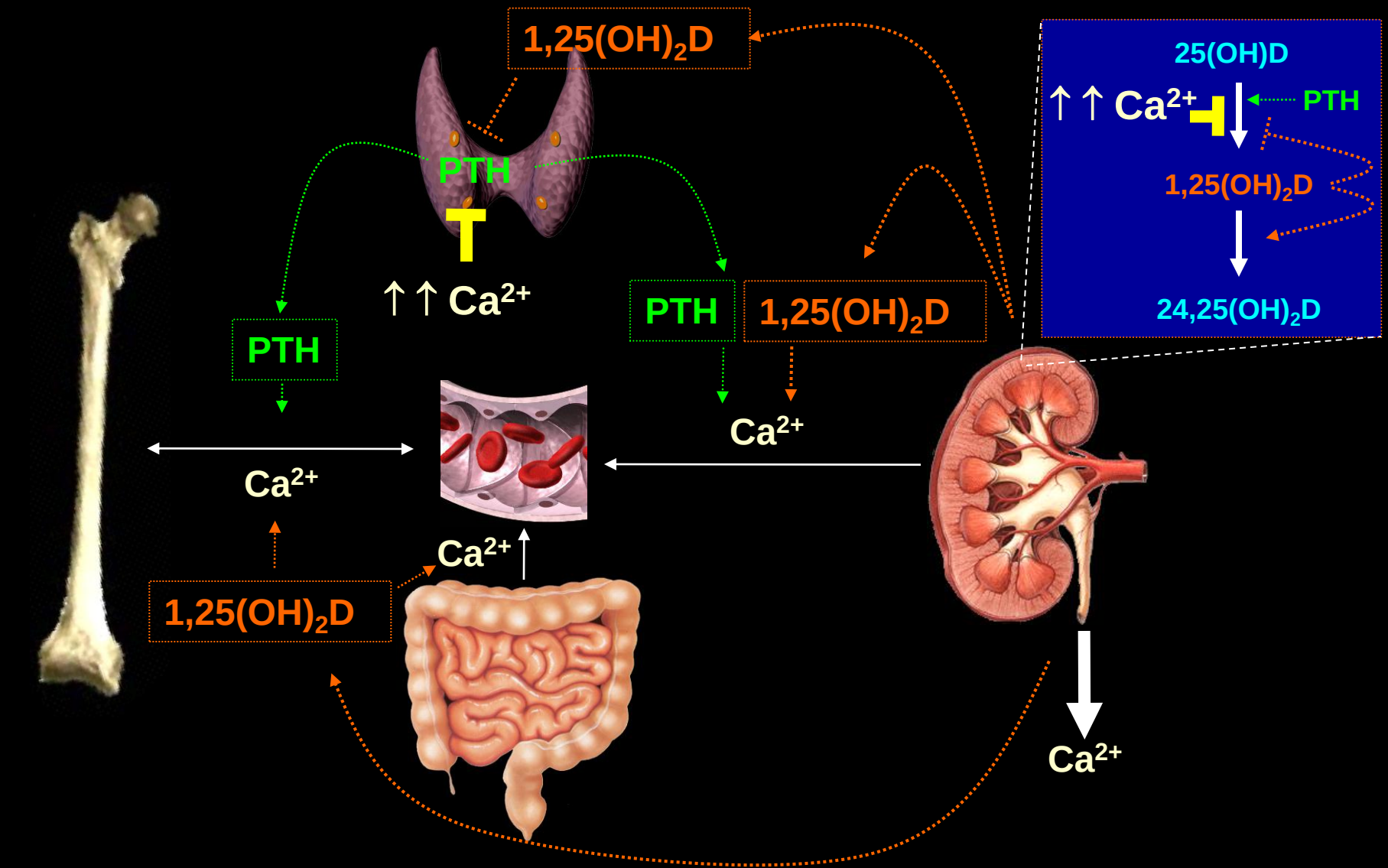
- **Parathyroid hormone**
- **1,25 $(OH)_2$Vitamin D**

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

- **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)

Biochemistry

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

$$\frac{\text{(Urinary } Ca^{2+} \text{ x Serum Creatinine)}}{\text{(Serum } Ca^{2+} \text{ x Urinary Creatinine)}}$$

Imaging

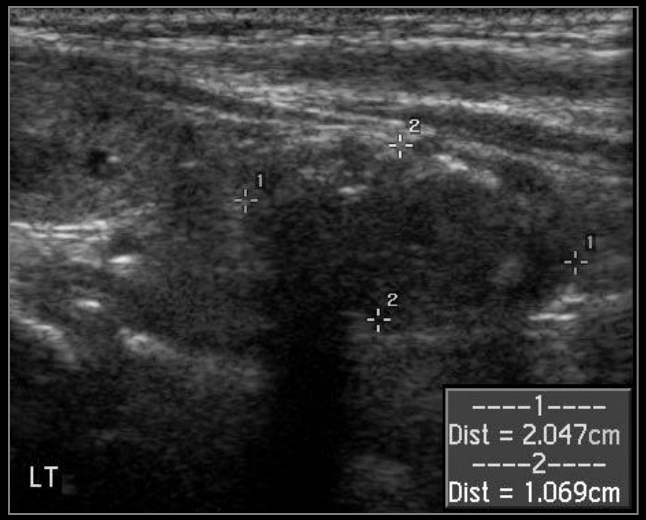
- Renal Ultrasound (Nephrolithiasis, Nephrocalcinosis)
- DXA scan (Decreased bone mineral density)

Localisation of parathyroid adenoma

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

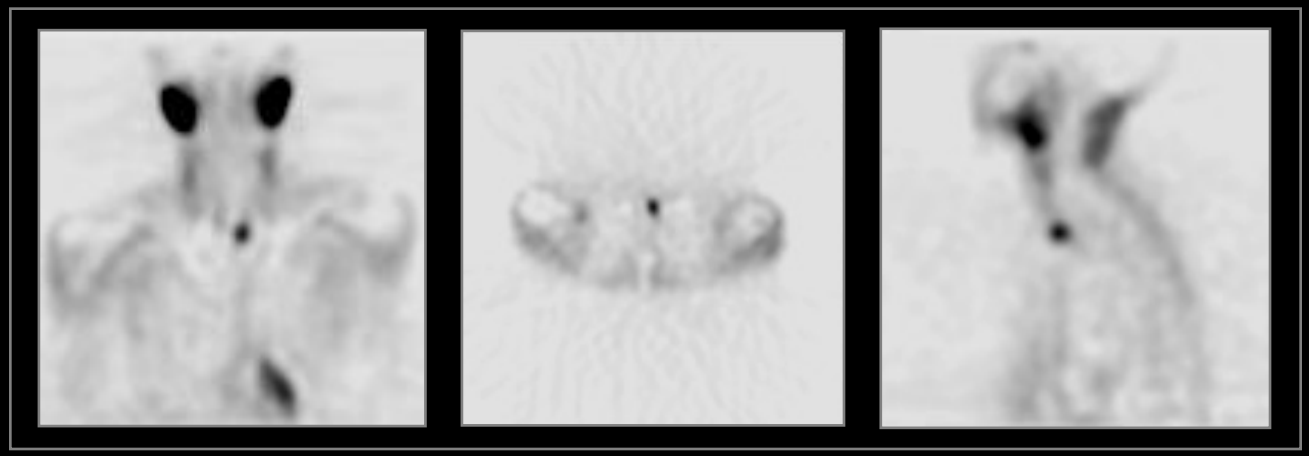
Parathyroid localisation

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)

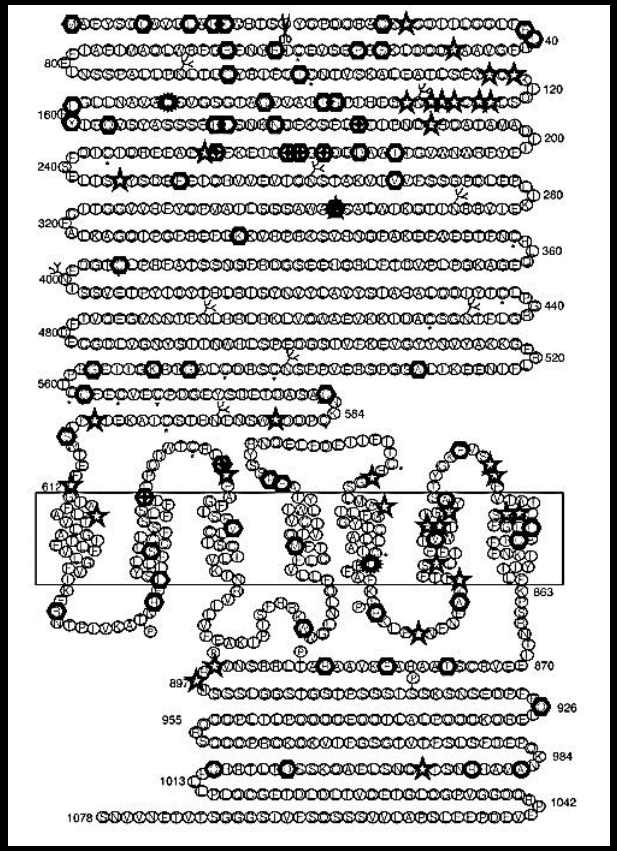
- Autosomal dominant (2% hypercalcaemia)
- Heterozygous loss of function mutations of *CASR*
- Increase in parathyroid gland calcium set-point
- Mild enlargement of parathyroids

Presentation

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

Management

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



CASR mutations

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

Other causes of hypercalcaemia

Local osteolytic hypercalcaemia (LOH)

- ↑↑ Ca^{2+}, ↓ PO_4^{3-}, ↑ALP,
- Undetectable PTH and PTHrP
- Bone scan identifies multiple skeletal metastases

Hypervitaminosis D (Excess $1,25(OH)_2D$ synthesis)

- ↑Ca^{2+}, ↑PO_4^{3-}, Undetectable PTH, →25-OHD, ↑$1,25(OH)_2D$
- Sarcoidosis, TB, IBD or any granulomatous diseases
  - (Macrophage 1α-hydroxylase activity)

Vitamin D excess (Pharmacological doses 25-OHD >40,000 IU/d)

- ↑Ca^{2+}, ↑PO_4^{3-}, Undetectable PTH, ↑↑25-OHD, →$1,25(OH)_2D$
- ↑uCa^{2+} and stones

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
- Vitamin D deficiency or resistance

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

Hypoparathyroidism (PTH deficiency)

- ↓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)

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

Genetic basis of pseudohypoparathyroidism (PHP)

Pseudohypoparathyroidism (Renal PTH resistance)

- **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**
- **Maternal GNAS allele is imprinted**
  - **Only the maternal allele is expressed in proximal renal tubule**

Actions of PTH in PCT are mediated by Gαs

- **If maternal GNAS allele is mutated or imprinting is defective 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

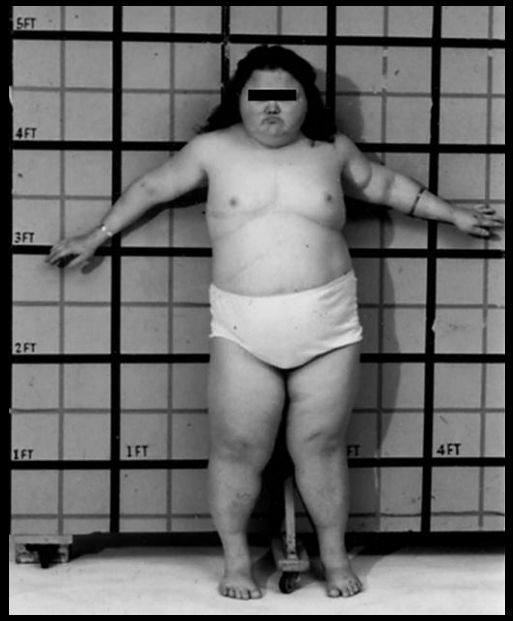
- **Mutation of either GNAS allele: Albrights Hereditary Osteodystrophy**

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

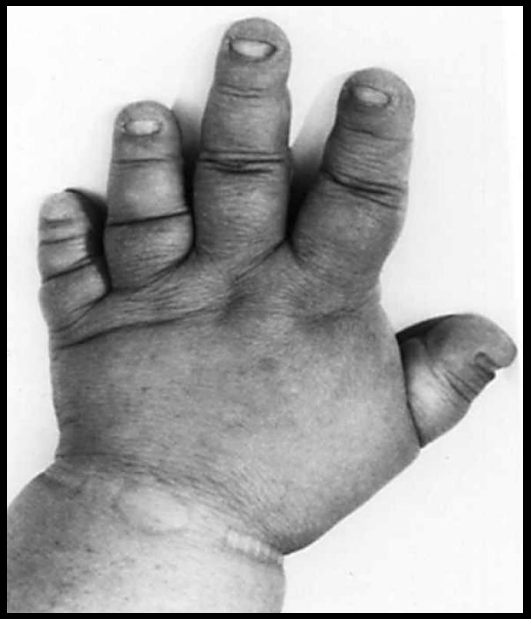
- **Primary hypothyroidism, hypogonadism and GH deficiency**

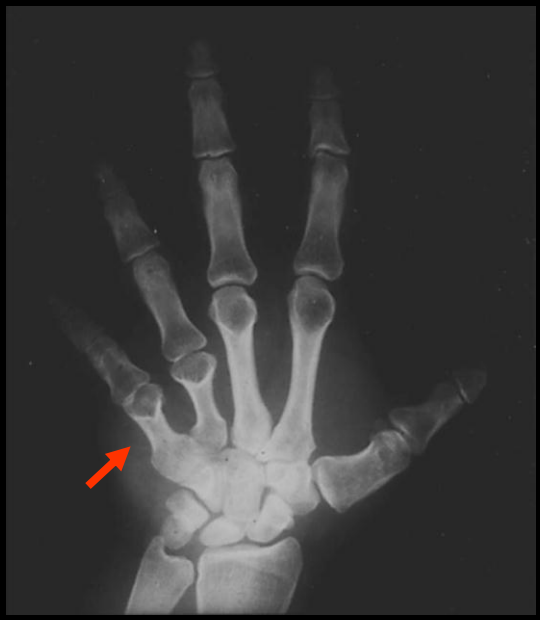
(Mantovani G (2006) Best Pract Res Clin Endocrinol Metab.20:501-13)

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

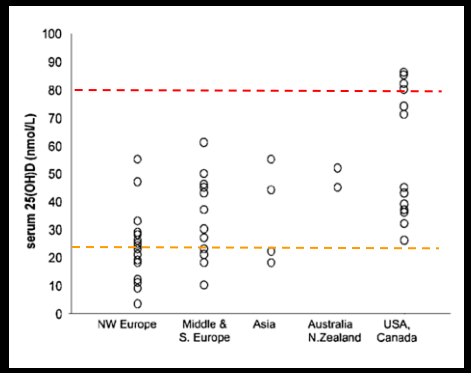
Maximum recommended daily dose 2000 IU

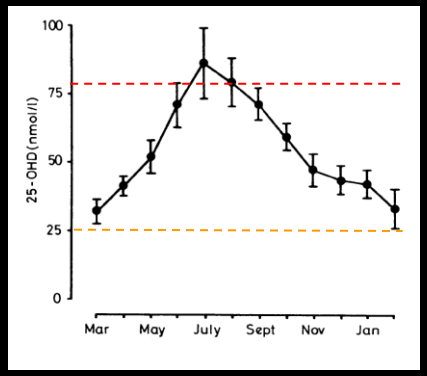
Vitamin D supplementation is the most commonly used medication in the world and is worth $1000 million per annum

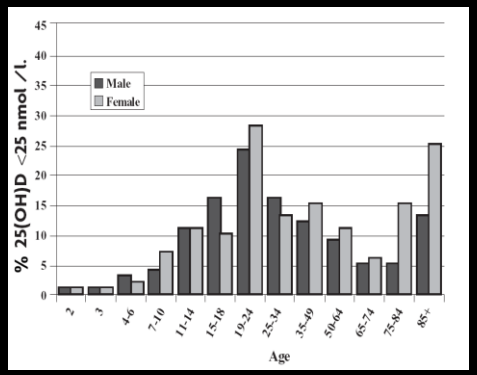
(Vieth R 2007 Am J Clin Nutr 85:649)

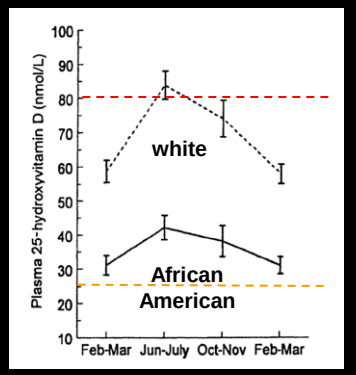
Vitamin D normal range?

25-OHD is 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









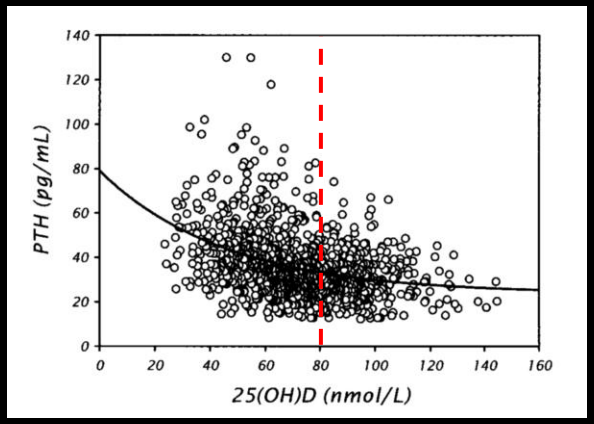
25-OHD$_3$ of <25nM have previously been considered suboptimal (DoH 1998)
Many now suggest that 25-OHD$_3$ should be 40nM or even >75-80nM

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

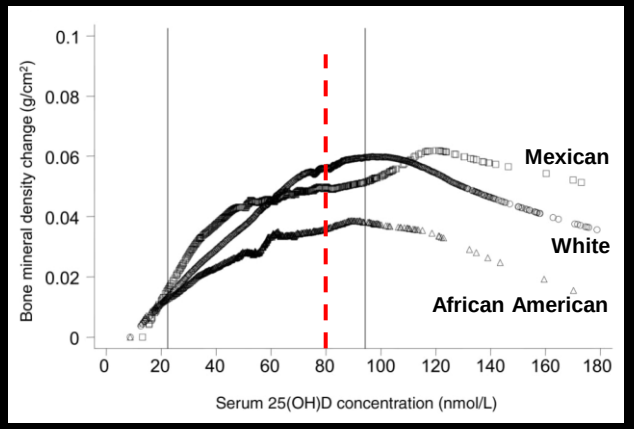
(Lips P 2001 Endo Rev 22:477-501; Juttmann JR et al 1981 BMJ 282:1349-1352; Jones G et al 2007 JBMR 22:v11-v15
Position statement by the Scientific Advisory Committee on Nutrition 2008)

Maintenance of vitamin D >80nM?

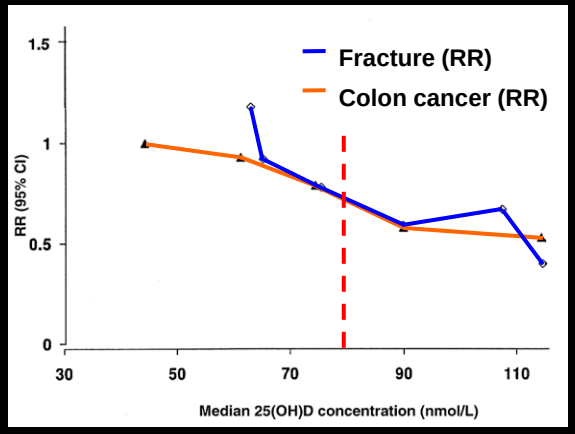
Maximum PTH suppression



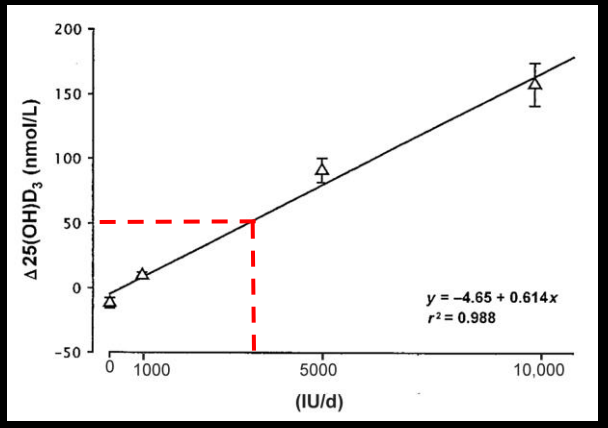
Peak BMD at 80-100mM



Reduces # and cancer risk



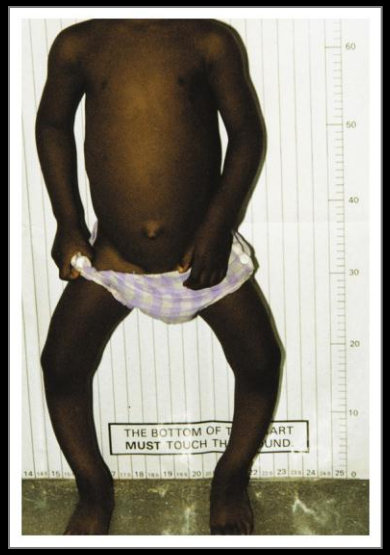
To maintain 25-OHD >80nM requires 3,000 - 4,000 IU/d

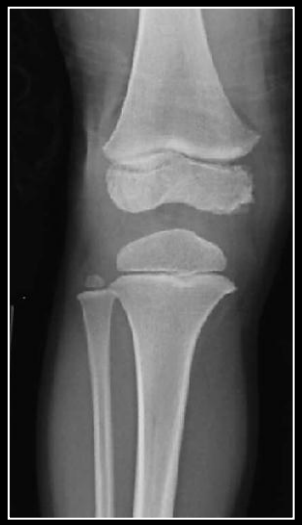


(Bischoff-Ferrari HA et al 2006 Am J Clin Nutr 84:18-28; Heaney RP 2003 Am J Clin Nutr 77:204-210)

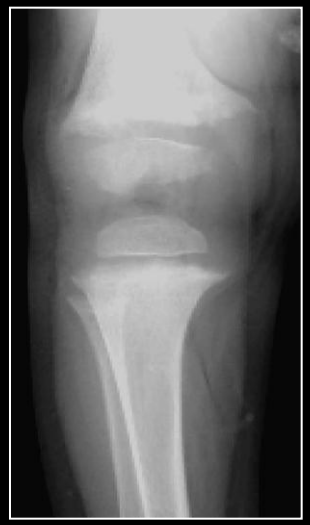
Rickets due to vitamin D deficiency

(low Ca^{2+} and PO_4^{3-})





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)

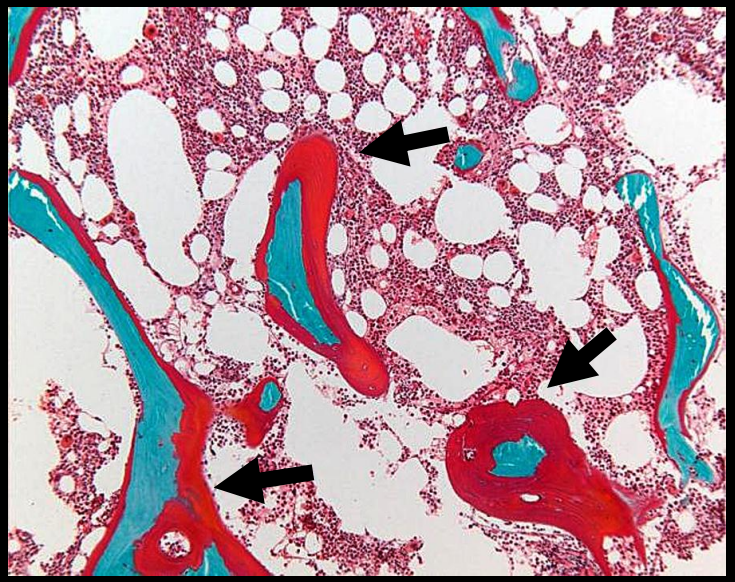
Rachitic rosary in ribs
Bone pain, muscle weakness, poor mobility
May have tetany and seizures

NEJM 2009 360(3)

Vitamin D deficiency in adults

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

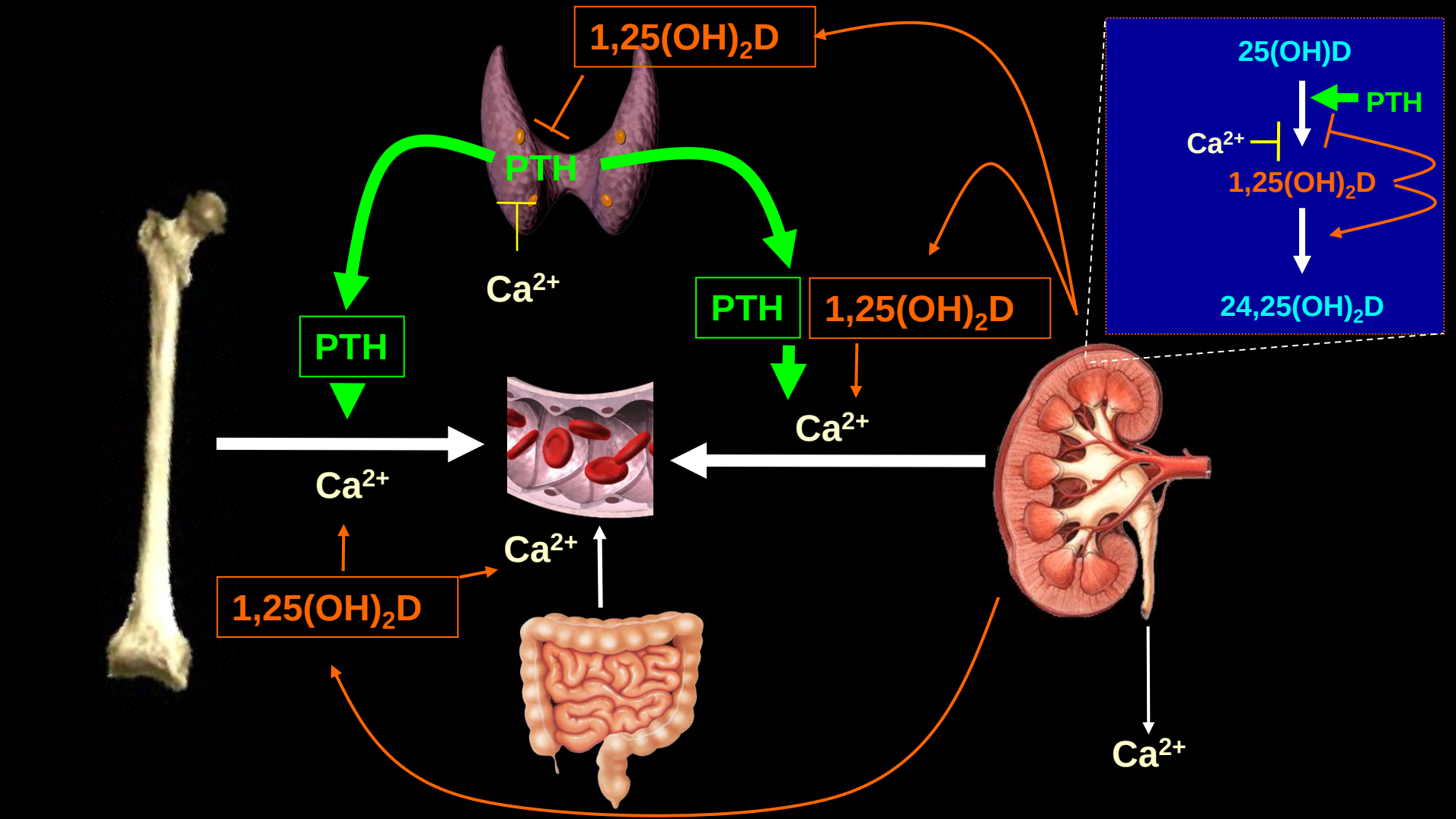
Mineralised osteoid in green



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

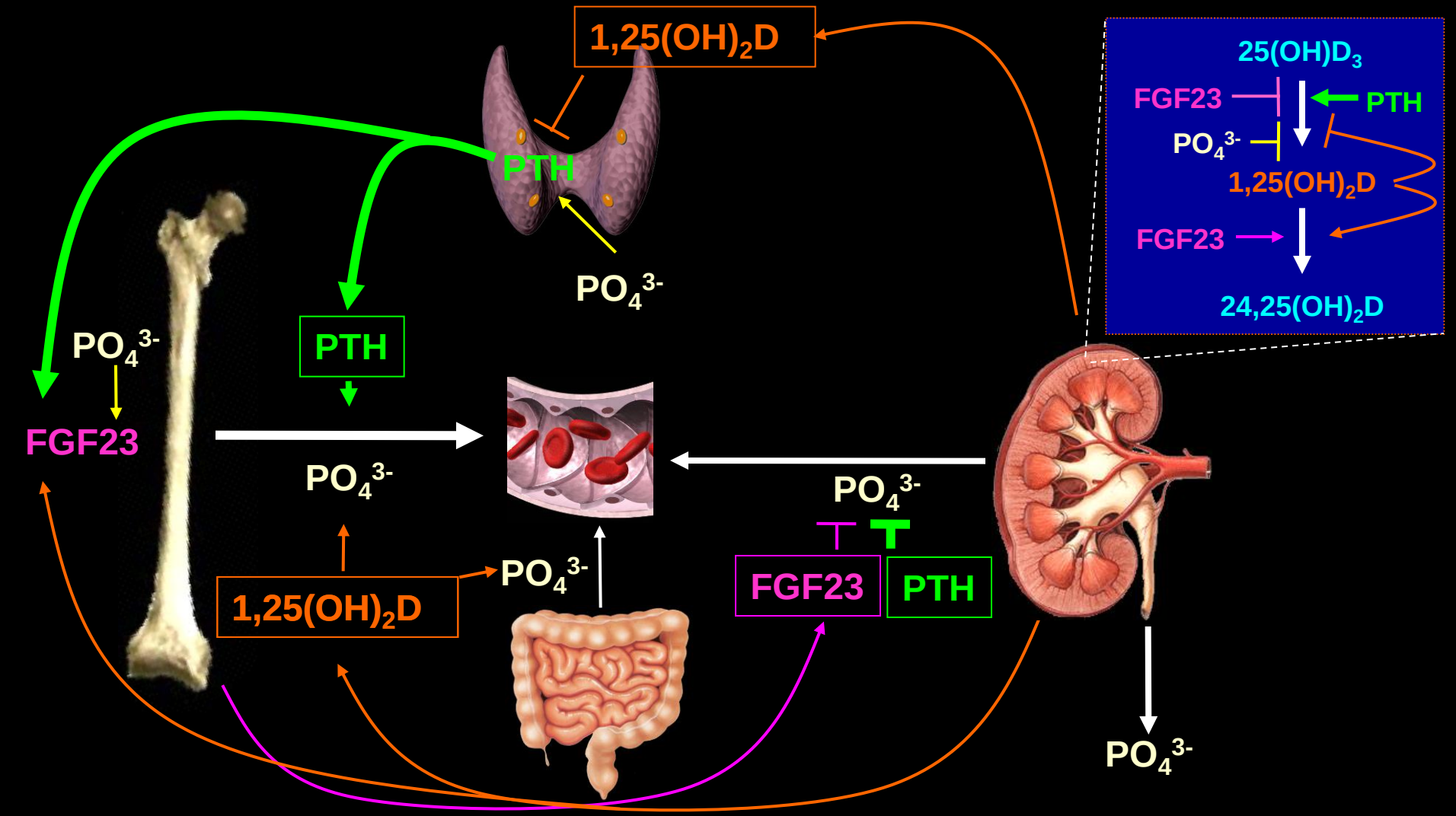


Low $1,25(OH)_2D$ reduces intestinal absorption of Ca^{2+}

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

Rare vitamin D related conditions

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

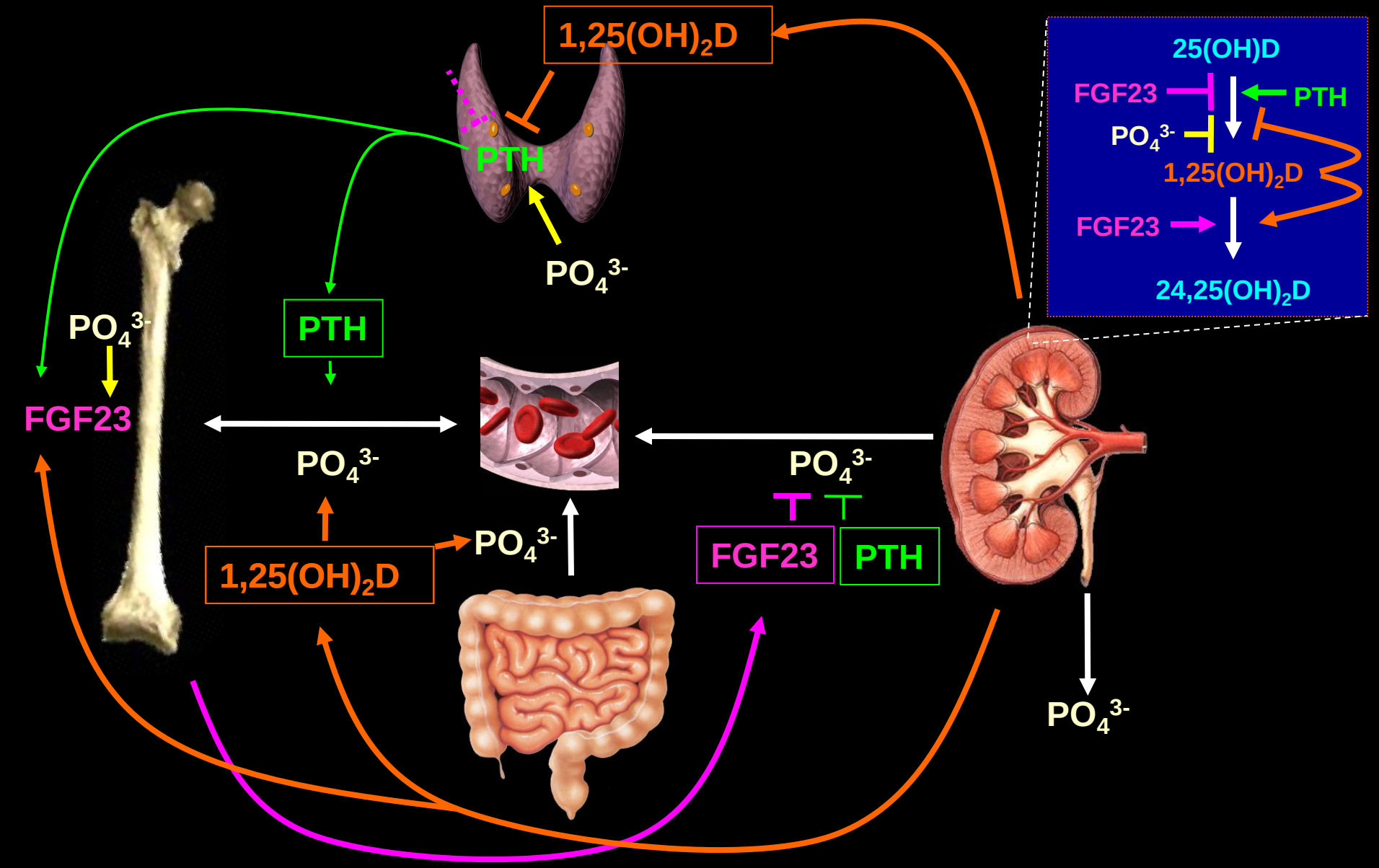
Rickets, growth retardation and alopecia

↓↓Ca^{2+}, ↓↓PO_4^{3-} , ↑PTH, →25-OHD and ↑$1,25(OH)_2D$

Rx high dose calcium cures the rickets

Disorders of phosphate homeostasis

Regulation of serum phosphate



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

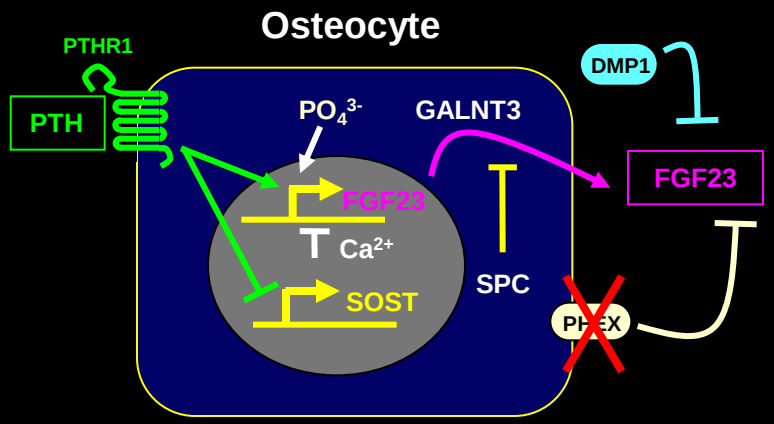
- Irritability, confusion seizures, coma
- Haemolysis and thrombocytopenia
- Muscle weakness, myopathy, rhabdomyolysis, cardiomyopathy
- Hypercalciuria and hypermagnesuria, glycosuria
- Impaired gluconeogenesis, Insulin resistance and hypoparathyroidism
- Metabolic acidosis

Mechanism

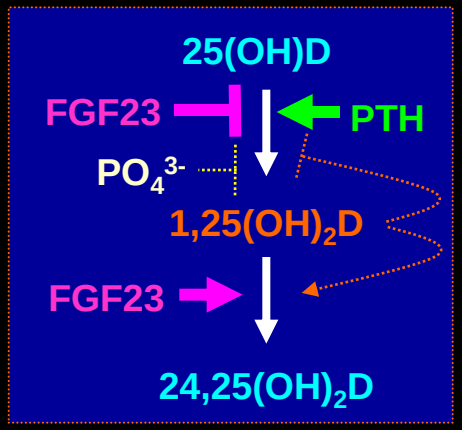
- Redistribution of PO_4^{3-} into cells
  - Increased synthesis of phosphorylated carbohydrates
- Increased renal excretion
  - ↑PTH, ↑FGF23, ↑KLOTHO
- Decreased intestinal absorption
  - Aluminium/magnesium antacids, chronic diarrhoea

X-linked hypophosphatemic rickets

(Enhanced FGF23 signalling)



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

Rare causes of hypophosphatemia

Tumour-induced osteomalacia (TIO)
($\downarrow PO_4^{3-}$, $\downarrow 1,25(OH)_2D$)
FGF23 secreted by benign tumour

McCune-Albrights Fibrodysplasia
($\downarrow PO_4^{3-}$, $\downarrow 1,25(OH)_2D$)
GNAS1 mosaic (FGF23 secreted by skeletal fibromas)

Autosomal dominant hypophosphataemic rickets (ADHR)
($\downarrow PO_4^{3-}$, $\downarrow 1,25(OH)_2D$)
FGF23 mutation prevents cleavage and its inactivation

Autosomal recessive hypophosphataemic rickets (ARHR)
($\downarrow PO_4^{3-}$, $\downarrow 1,25(OH)_2D$)
DMP1 loss of function mutation impairs FGF23 signalling

Hereditary hypophosphataemia rickets and hypercalciuria (HHRH)
($\uparrow Ca^{2+}$, $\downarrow PO_4^{3-}$, $\uparrow\uparrow 1,25(OH)_2D$ rickets, $\uparrow uPO_4^{3-}$, $\downarrow uCa^{2+}$)
Sodium phosphate co-transporter NaPiIIc mutation (SCL34A3)

Hypophosphataemic Nephrolithiasis and Osteoporosis (HNO)
($\uparrow Ca^{2+}$, $\downarrow PO_4^{3-}$, $\uparrow\uparrow 1,25(OH)_2D$, $\uparrow uPO_4^{3-}$ but no rickets)
Sodium phosphate co-transporter NaPiIIa mutation (SCL34A1)

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**

Chronic kidney disease-Mineral bone disorder

Phosphate homeostasis in CKD

Highest FGF23 levels are found inn 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

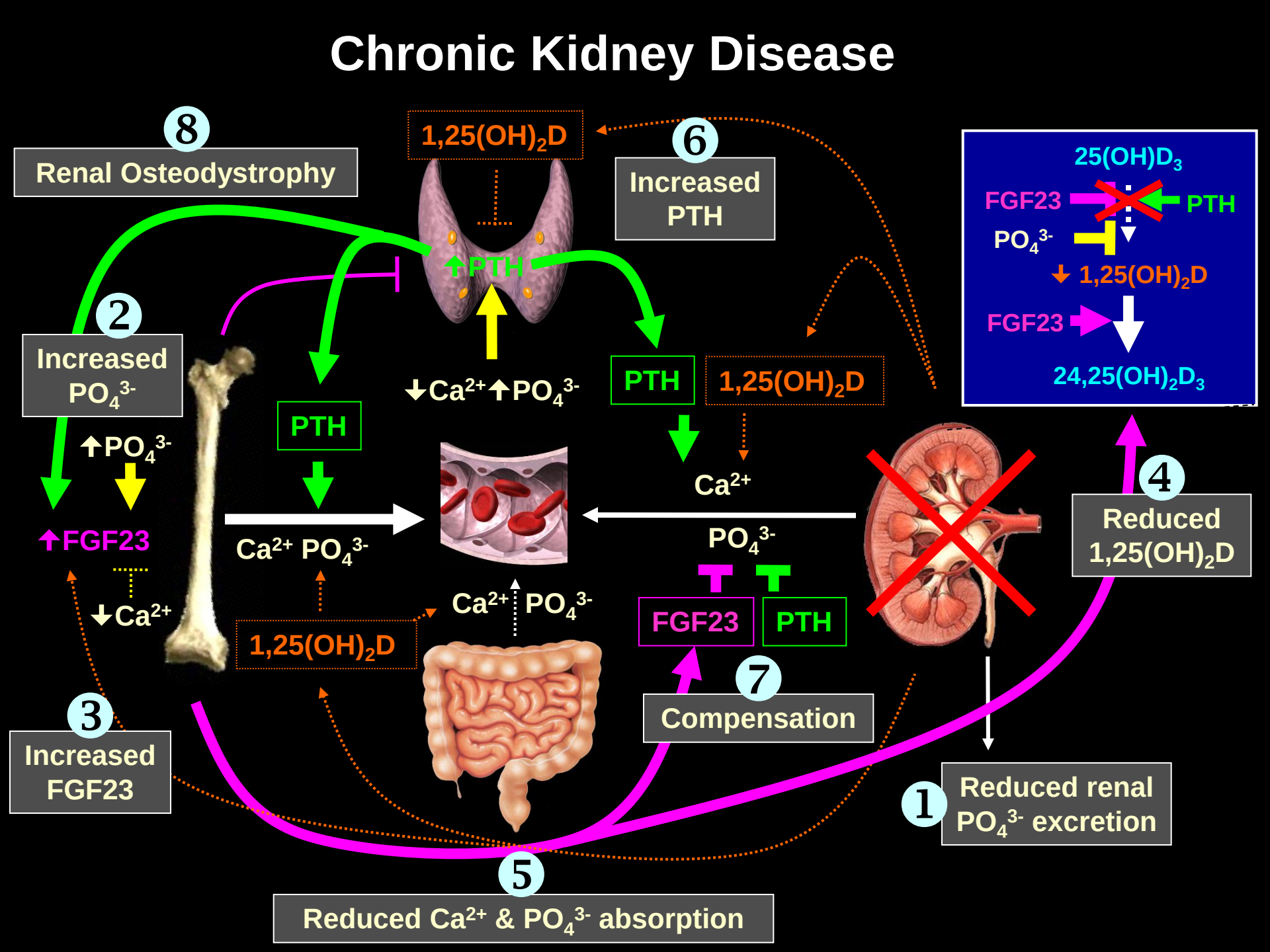
Hyperphosphataemia despite extremely high FGF23 levels

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 stage3 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)

Hyperparathyroidism in CKD

If parathyroid hyperplasia results in parathyroid autonomy
- Calcitriol will not suppress PTH
- Calcitriol treatment may result in hypercalcaemia

Management hyperparathyroidism
- Cinacalcet (CaSR agonist)
  - Inhibit PTH synthesis and release
  - Lowers PTH and Ca^{2+}

Indications for subtotal parathyroidectomy
- Persistent hypercalcaemia
- High Ca^{2+} and PO_4^{3-} product and soft tissue calcification,
- Severe pruritus
- High bone turnover
- Tertiary hyperparathyroidism
  - Severe progressive and symptomatic hyperparathyroidism

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General

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Pseudohypoparathyroidism

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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.

Table 3. Strategies to Prevent and Treat Vitamin D Deficiency.*

Cause of Deficiency†	Preventive and Maintenance Measures to Avoid Deficiency	Treatment of Deficiency
Children		
Breast-feeding without vitamin D supplementation[28,33,89,104] — up to 1 yr	400 IU of vitamin D_3/day,[1,28,104] sensible sun exposure,[1] 1000–2000 IU of vitamin D_3/day is safe,[1,2,27,75] maintenance dose is 400–1000 IU of vitamin D_3/day[1,2,104]	200,000 IU of vitamin D_3 every 3 mo,[1,105] 600,000 IU of vitamin D intramuscularly, repeat in 12 wk[106]; 1000–2000 IU of vitamin D_2 or vitamin D_3/day[1,107] with calcium supplementation
Inadequate sun exposure[24,29-31,108] or supplementation,[1,28,104-107] dark skin[23] — 1 through 18 yr	400–1000 IU vitamin D_3/day,[1,104,107] sensible sun exposure, 1000–2000 IU of vitamin D_3/day[1,108] is safe,[1,27,75,104,107] maintenance dose is 400–1000 IU of vitamin D/day[1,75]	50,000 IU of vitamin D_2 every wk for 8 wk[1,9]‡
Adults		
Inadequate sun exposure[7,15] or supplementation,[7-20] decreased 7-dehydrocholesterol in skin because of aging (over 50 yr)[7]	800–1000 IU of vitamin D_3/day,[1-3,8,16,21,42] 50,000 IU of vitamin D_2 every 2 wk or every mo,[7,9] sensible sun exposure[7,15,109,110] or use of tanning bed or other UVB radiation device (e.g., portable Sperti lamp),[111-114] up to 10,000 IU of vitamin D_3/day is safe for 5 mo,[27] maintenance dose is 50,000 IU every 2 wk or every mo[7,9]‡	50,000 IU of vitamin D_2 every wk for 8 weeks[9]; repeat for another 8 wk if 25-hydroxyvitamin D <30 ng/ml‡
Pregnant or lactating (fetal utilization,[33] inadequate sun exposure[33,89] or supplementation[33,89])	1000–2000 IU of vitamin D_3/day,[33,89] 50,000 IU of vitamin D_2 every 2 wk, up to 4000 IU of vitamin D_3/day is safe for 5 mo,[33,89] maintenance dose is 50,000 IU of vitamin D_2 every 2 or 4 wk[9]‡	50,000 IU vitamin D_2 every wk for 8 wk[115]; repeat for another 8 wk if 25-hydroxyvitamin D <30 ng/ml‡
Malabsorption syndromes (malabsorption of vitamin D,[2,3,86,87] inadequate sun exposure[2,3,6,7] or supplementation[2,3,6,7])	Adequate exposure to sun or ultraviolet radiation,[7,113] 50,000 IU of vitamin D_2 every day, every other day, or every wk,† up to 10,000 IU of vitamin D_3/day is safe for 5 mo,[27] maintenance dose is 50,000 IU of vitamin D_2 every wk‡	UVB irradiation (tanning bed or portable UVB device, e.g., portable Sperti lamp),[111-114] 50,000 IU of vitamin D_2 every day or every other day‡
Drugs that activate steroid and xenobiotic receptor,[88] and drugs used in transplantation[116]	50,000 IU of vitamin D_2 every other day or every week, maintenance dose is 50,000 IU of vitamin D_2 every 1, 2, or 4 wk‡	50,000 IU of vitamin D_2 every 2 wk for 8–10 wk, or every wk if 25-hydroxyvitamin D <30 ng/ml‡
Obesity[2,7]	1000–2000 IU of vitamin D_3/day, 50,000 IU of vitamin D_2 every 1 or 2 wk, maintenance dose is 50,000 IU of vitamin D_2 every 1, 2, or 4 wk‡	50,000 IU of vitamin D_2 every wk for 8–12 wk; repeat for another 8–12 wk if 25-hydroxyvitamin D <30 ng/ml‡
Nephrotic syndrome[2,3,6,7,91-94]	1000–2000 IU of vitamin D_3/day, 50,000 IU of vitamin D_2 once or twice/wk,[2,94] maintenance dose is 50,000 IU of vitamin D_2 every 2 or 4 wk[2]‡	50,000 IU of vitamin D_2 twice/wk for 8–12 wk[2,94]; repeat for another 8–12 wk if 25-hydroxyvitamin D <30 ng/ml‡
Chronic kidney disease§		
Stages 2 and 3	Control serum phosphate,[6] 1000 IU of vitamin D_3/day, 50,000 IU of vitamin D_2 every 2 wk,[91,94] maintenance dose is 50,000 IU of vitamin D_2 every 2 or 4 wk; may also need to treat with an active vitamin D analog when vitamin D sufficiency is obtained‡	50,000 IU of vitamin D_2 once/wk for 8 wk[91,94]; repeat for another 8 wk if 25-hydroxyvitamin D <30 ng/ml‡
Stages 4 and 5	1000 IU of vitamin D_3/day,[51] 50,000 IU of vitamin D_2 every 2 wk, need to treat with 1,25-dihydroxyvitamin D_3 or active analogue‡	0.25–1.0 μg of 1,25-dihydroxyvitamin D_3 (calcitriol)[2,6,91,93,94] by mouth twice a day or one of the following: 1–2 μg of paricalcitriol IV every 3 days,[6,91,93,94] 0.04–0.1 μg/kg IV every other day initially and can increase to 0.24 μg/kg, 2–4 μg by mouth three times/wk,[6,91,93,94] or doxecalciferol[6,91,93,94] 10–20 μg by mouth three times/wk or 2–6 μg IV three times/wk
Primary or tertiary hyperparathyroidism	800–1000 IU of vitamin D_3/day, 50,000 IU of vitamin D_2 every 2 wk (serum calcium levels will not increase),[115] maintenance dose is 50,000 IU of vitamin D_2 every 2 or 4 wk‡	50,000 IU of vitamin D_2 once a wk for 8 wk; repeat for another 8 wk if 25-hydroxyvitamin D <30 ng/ml
Granulomatous disorders and some lymphomas	400 IU of vitamin D_3/day, maintenance dose is 50,000 IU of vitamin D_2/mo‡	50,000 IU vitamin D_2 once a wk for 4 wk or every 2 to 4 wk, need to keep 25-hydroxyvitamin D between 20 and 30 ng/ml (level above 30 ng/ml can result in hypercalciuria and hypercalcemia)‡

Vitamin D Preparations

Ergocalciferol (D_2) 400IU
100mg Calcium
Cholecalciferol (D_3) 200IU
500mg Calcium
Cholecalciferol (D_3) 400IU
500mg Calcium

Ergocalciferol (D_2)
10,000IU PO
50,000IU PO
300,000IU IM

1α-OHD_3
250ng, 500ng, 1μg PO
2μg/ml drops or injection

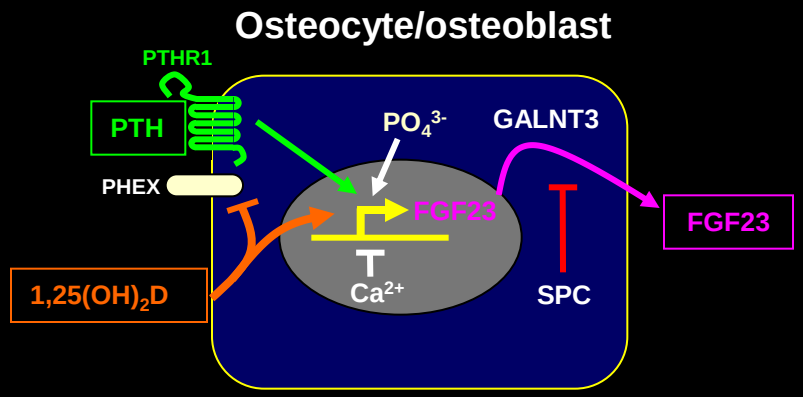
1,25$(OH)_2D_3$
250ng, 500ng PO
1μg/ml injection

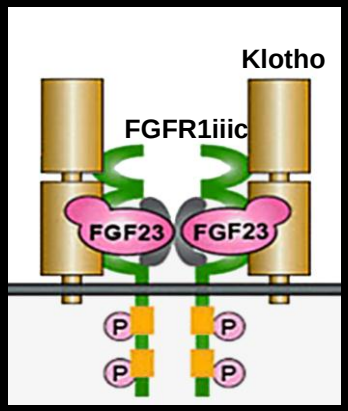
(Holick MF 2007 NEJM 357:266-281)

Hyperphosphatemic familial tumoral calcinosis

Hyperphosphatemic familial tumoral calcinosis (HFTC)

(Impaired FGF23 signalling)





Hyperphosphatemic familial tumoral calcinosis (Impaired FGF23 signalling)

Autosomal recessive: loss of function mutations of FGF23, GALNT3 or KLOTHO

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

Rx low phosphate diet and phosphate binders

Mutations in pseudohypoparathyroidism

Within a family

Pseudo-pseudohypoparathyroidism (PPHP)

Paternal inheritance of inactivating mutations of Gαs

AHO (one *GNAS* allele is mutated)

No PTH resistance (normal calcium)

Pseudohypoparathyroidism 1A (PHP1A)

Maternal inheritance of inactivating mutations of Gαs

AHO (one *GNAS* allele is mutated)

PTH resistance (↓Ca^{2+}, ↑PO_4^{3-}, ↑PTH)

Variable resistance to TSH, FSH, LH, GHRH & Glucagon

(ACTH or ADH resistance never reported)

In other families

Pseudohypoparathyroidism 1B (PHP1B)

Maternal inheritance but no mutations in Gαs coding region

No AHO (Both GNAS alleles are normal)

PTH resistance alone (↓Ca^{2+}, ↑PO_4^{3-}, ↑PTH),

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

$G\alpha_s$ expression in proximal tubule