Disorders of Calcium

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Calcium

99% is stored in bone or dentition

1% in extracellular fluid

50% - ionised form

40%- protein-bound

10% bound to anions (bicarbonate, citrate, phosphate, lactate)

Measurement

2.25-2.75mmol/l (each 1g/dl albumin binds 0.2mmol Ca)

Ca +0.02(40-patient albumin)

ionised , 1-1.5mmol/l (0.1 fall in pH increases by 0.05mmol)

Function of calcium

Skeletal and dental structure

Rickets, osteoporosis, fractures, dental caries

Muscle contraction and relaxation

cramps, muscle weakness, myopathy, laryngeal spasm

Stimulation of blood clotting

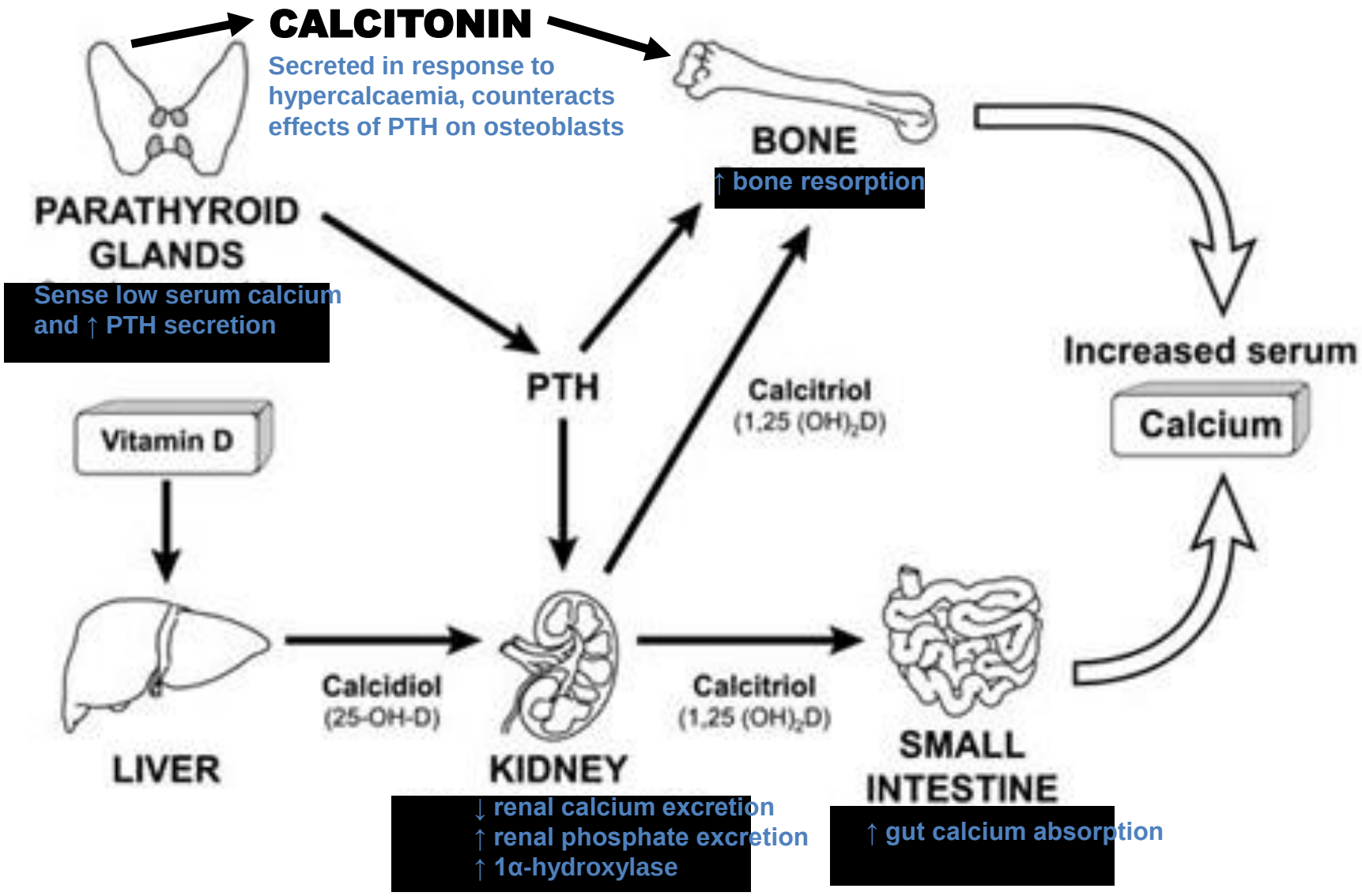
citrated blood

Nerve transmission

Tetany, seizures, perioral numbness and paraesthesia, stridor, *prolongation of QT interval, VF and heart block*

Maintenance of cell membrane integrity

Regulation of serum calcium

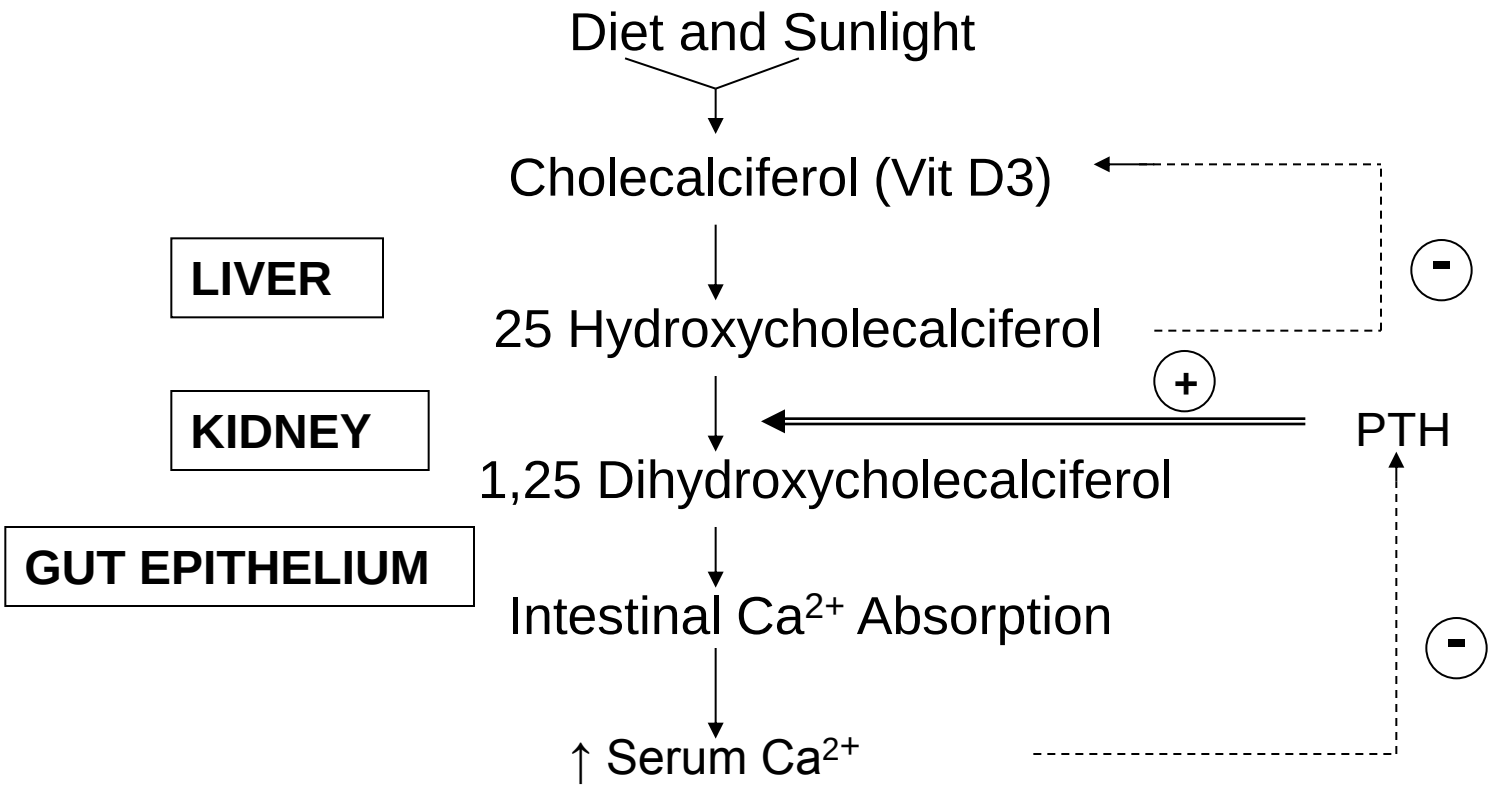


Vitamin D

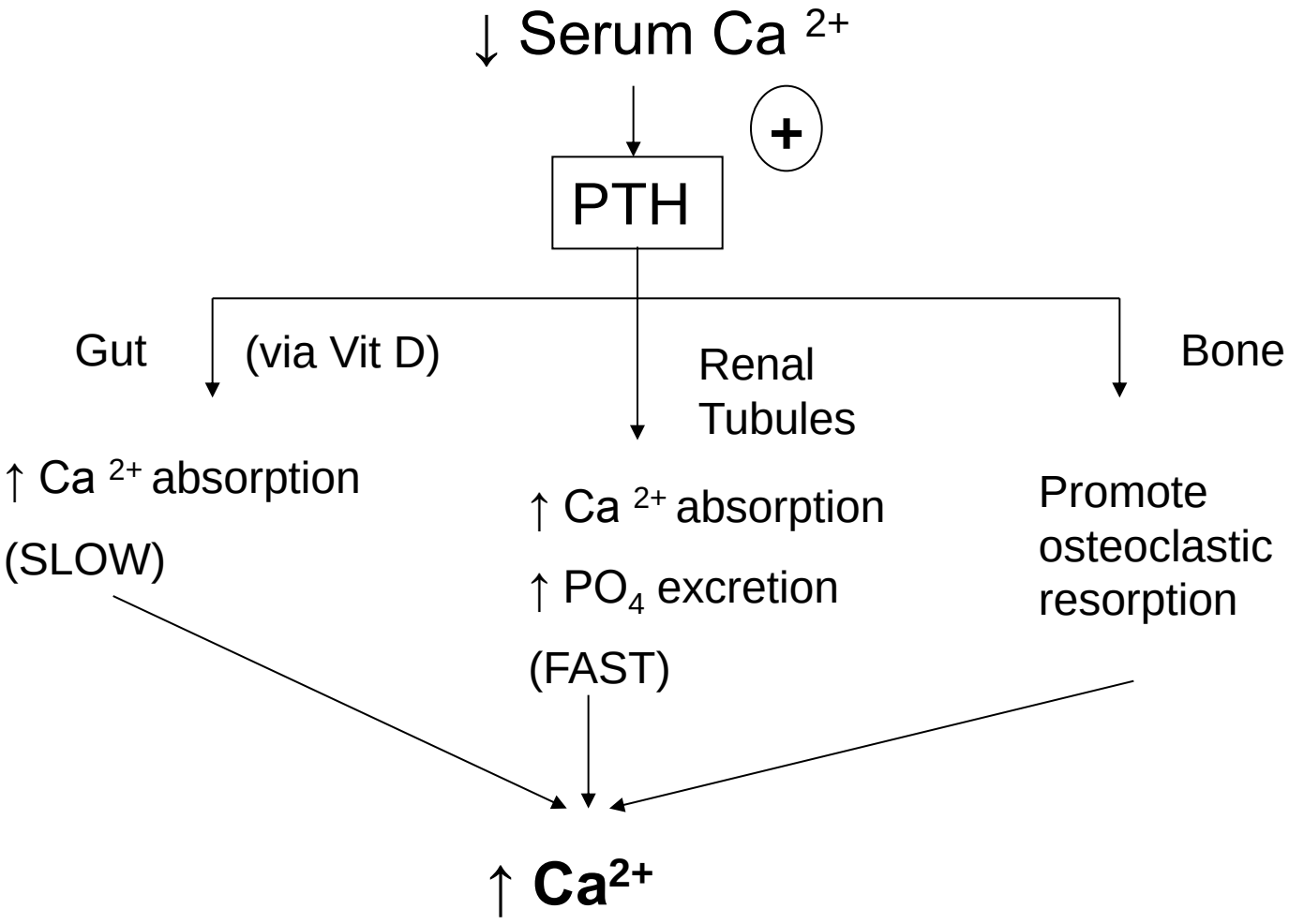
Promotes intestinal Ca^{2+} absorption

Mobilizes Ca^{2+} from bone (in presence of PTH)

Increases renal tubular Ca^{2+} reabsorption



Actions of PTH



MAGNESIUM

55% ionized]

15% complexed to anions] freely filterable

30% protein bound

Ionized form physiologically important

Protein bound form influenced by pH (like Ca^{2+})

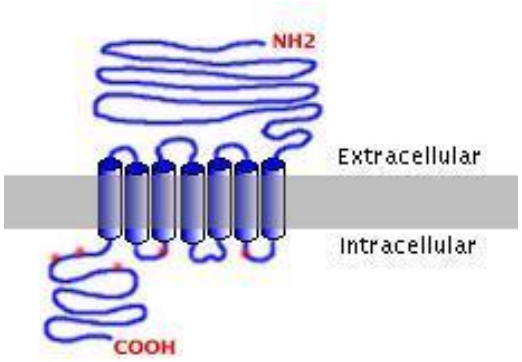
95% of glomerular filtrate is reabsorbed

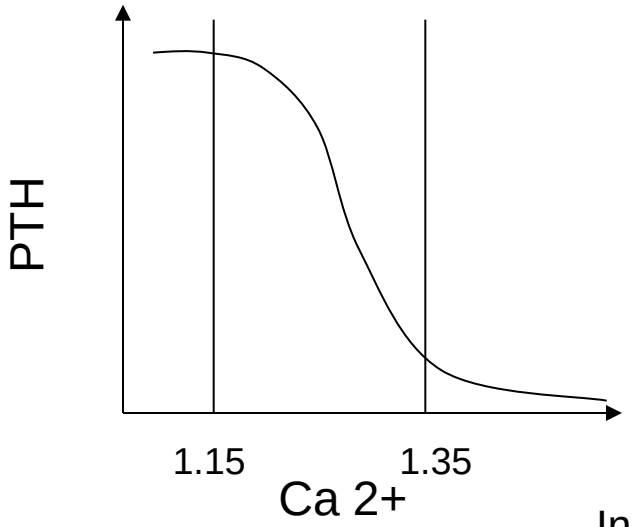
Serum Mg 1.8 – 2.2 mg/dL

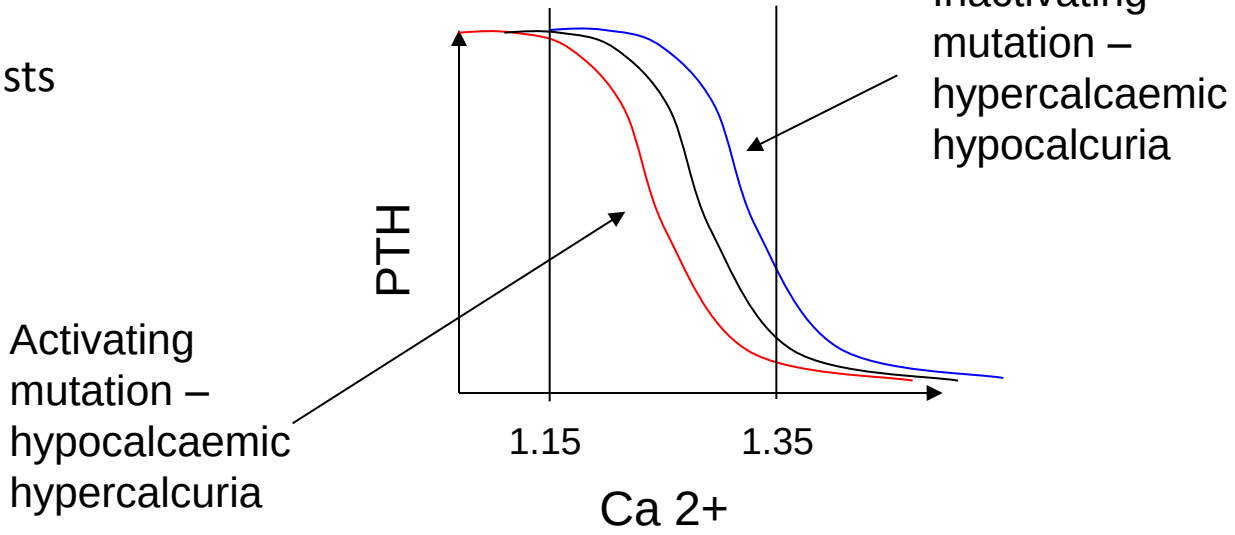
Normal levels required for PTH synthesis and action

Ca-sensing Receptor (CaSR)

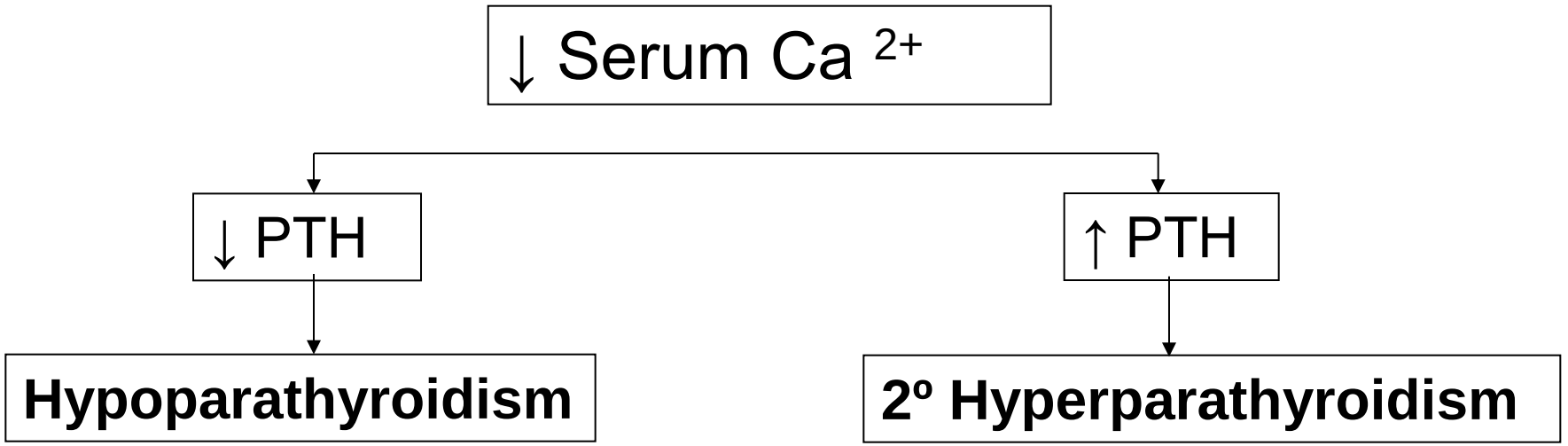
- G-protein coupled receptor
- Expressed in a range of cells
  - Parathyroid
  - Kidney
  - Osteoblasts







Hypocalcaemia



- Autoimmune (APS)
- Congenital (Di George)
- Mg deficiency
- CaSR mutations
- Post surgical
- Reduced phosphate

Nephrotic syndrome
Pancreatitis

- Vitamin D Metabolism

. PHP

- ARF/ CRF
- Tumour lysis
- Tubular disorders
- Drugs

Vitamin D metabolism

Lack of Vitamin D ‘ primary vitamin D deficiency’
(dietary, poor sunlight exposure)

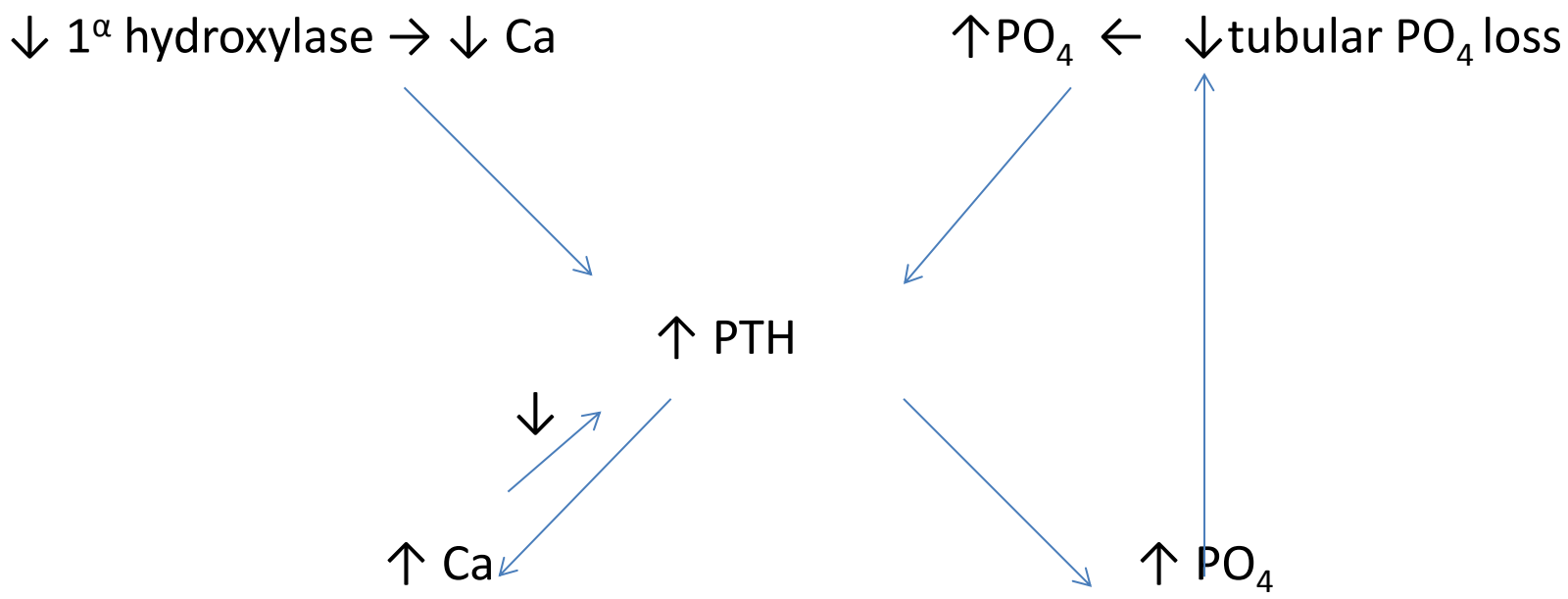
Lack of Vitamin D ‘secondary’
(malabsorbtion)

Abnormal vitamin D metabolism
(renal disease, liver disease, enzyme deficiency, PTH def)

Abnormal vitamin D action
(end-organ insensitivity)

Lack of calcium

Renal failure



CaSR MUTATIONS

Activating Mutations

$\rightarrow$ receptor sensitive to even low levels of Ca^{2+}

$\rightarrow$ inappropriate $\downarrow$ PTH level for serum Ca^{2+}

Mutation of same receptor in kidney $\rightarrow$ senses $\uparrow$ Ca^{2+} $\rightarrow$ inappropriate $\uparrow$ urinary Ca^{2+} excretion despite hypocalcaemia

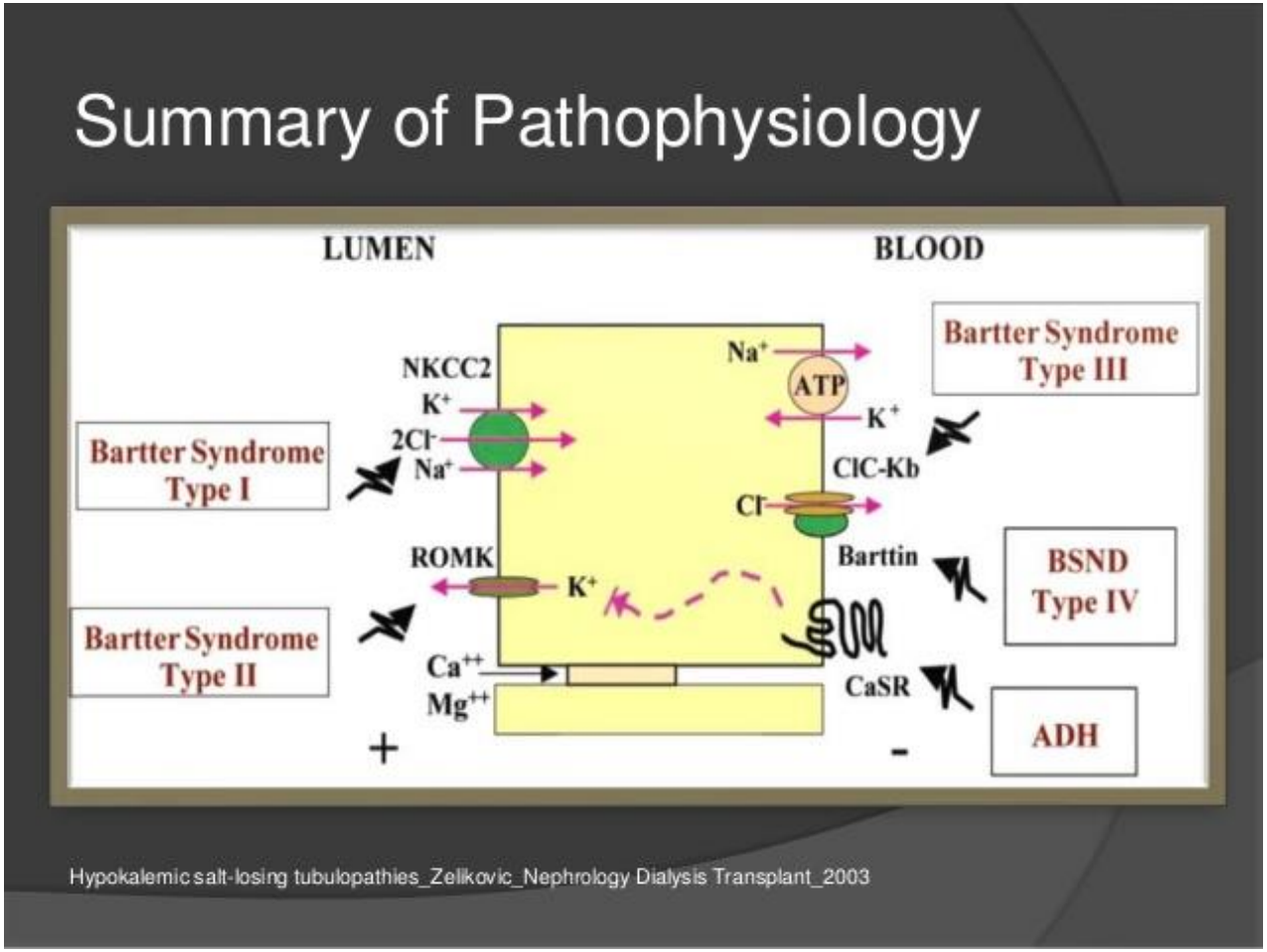
HYPOCALCAEMIA WITH PARADOXICAL HYPERCALCIURIA (PTH low)

Tubular Disorders

Bartters syndrome

Name	Bartter type	Associated gene mutations	Defect
neonatal Bartter's syndrome	type 1	SLC12A2 (NKCC2)	Na-K-2Cl symporter
neonatal Bartter's syndrome	type 2	ROMK/KCNJ1	thick ascending limb K^+ channel
classic Bartter's syndrome	type 3	CLCNKB	Cl^- channel
Bartter's syndrome with sensorineural deafness	type 4	BSND	Cl^- channel accessory subunit
Bartter's syndrome associated with autosomal dominant hypocalcemia	type 5	CASR	activating mutation of the calcium-sensing receptor
Gitelman's syndrome	-	SLC12A3 (NCCT)	Sodium-chloride symporter

Bartter's syndrome



Tubular Disorders

Familial Hypomagnesemia with hypercalciuria and nephrocalcinosis

Rare

Present 1-8

Renal failure

Claudins- involved in the paracellular reabsorption of Ca and Mg

CLDN19

Hypomagnesemia, hypercalciuria, nephrocalcinosis

UTI, polyuria, renal stones, enuresis,

FTT, seizures, tetany

Macular coloboma, retinitis pigmentosa, nystagmus or visual loss

Tubular Disorders

Familial Hypomagnesemia with hypercalciuria and nephrocalcinosis

CLDN16

Without ocular abnormalities

Other features

(hyperuricaemia, hypocitraturia , distal RTA, high PTH)

Management

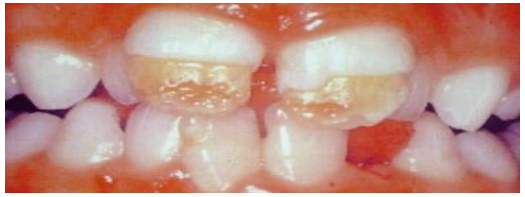
Genetic diagnosis/ genetic counselling

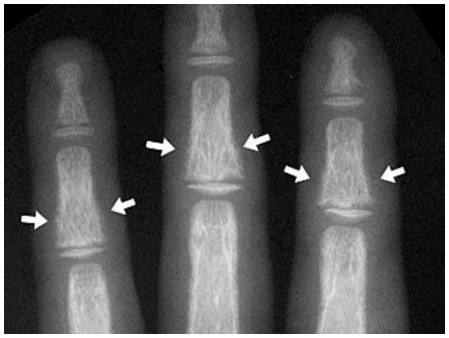
Supportive- Mg supplementation in large doses, reduce stone formation, ? Thiazides

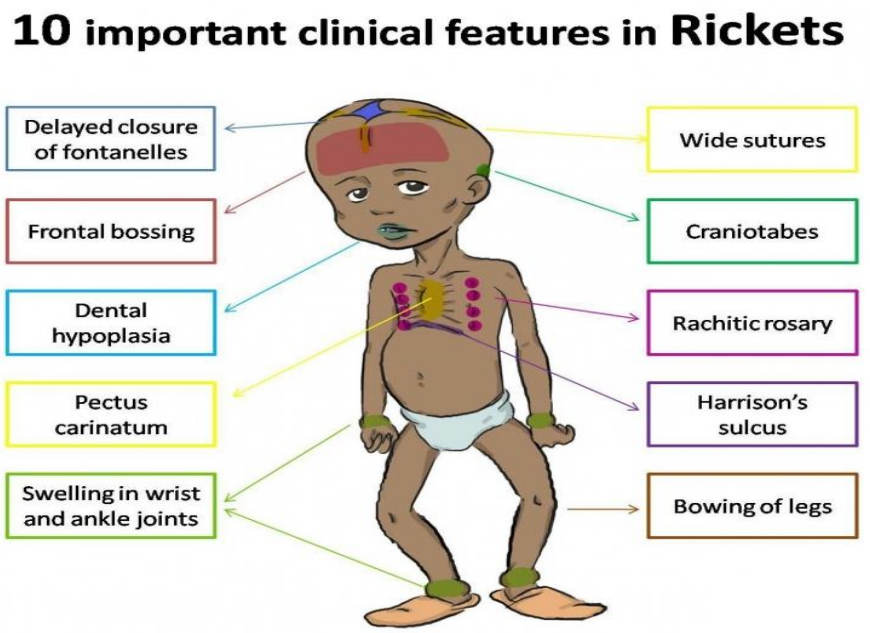
Renal Transplant

50% in ESRF by age 20

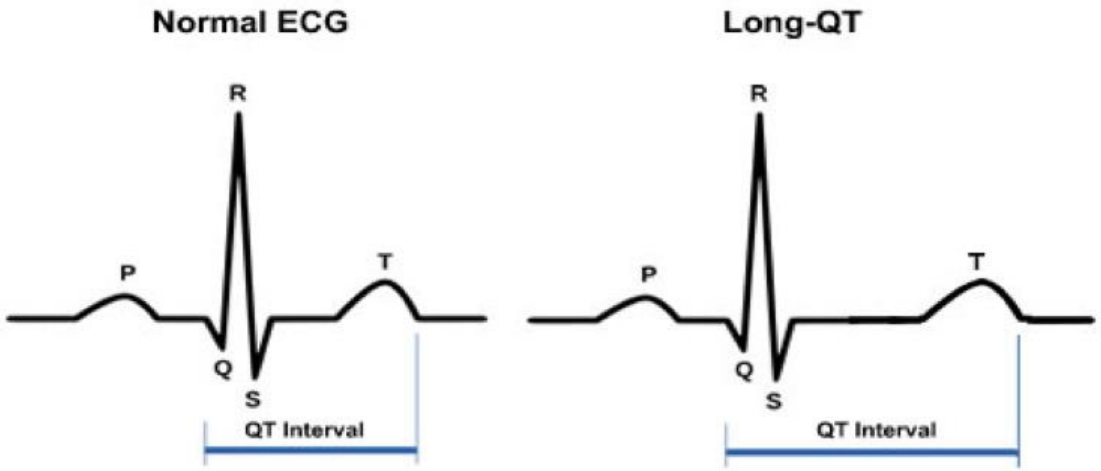
Clinical Features







Clinical Features



Clinical Symptoms

Neuromuscular-	tetany, seizures, muscle cramps and myopathy, perioral numbness and paresthesia, irritability
Respiratory-	stridor, bronchospasm, resp arrest
Cardiovascular-	syncope, prolongation of QT, heart block and VF
Eyes	cataract
Bone	rickets, poor dentition
Skin	dry coarse skin, brittle nails, alopecia

Clinical Case

History

13 year old girl, no past history of renal disease. General tiredness.

Examination

Small; normotensive, mild muscle weakness, urinary sediment unremarkable

Investigations

Creatinine 1469µmol/l, urea 59mmol/l, k 4.2mmol/l, bicarbonate 9 mmol/l

Ca 1.12mmol/l, Phosphate 4.4 mmol/l, albumen 36g/l, PTH 275pmol/l (1.1-6.9)

(Ca x PO_4 4.9)

US- small shrunken kidneys with cortical cysts

Clinical Case

Management

Reduce phosphate intake

Correct calcium – intravenous calcium

Correct acidosis- oral bicarbonate

Theatre- Permcath for haemodialysis (first session 3 days following admission)

Phosphate 2.51, Ca 1.76 (Ca x PO_4 4.4)

Commenced alfacalcidol, phosphate binders)

Ca normal pre dialysis at 7 days

PTH 1.5x upper limit of normal at 7 months

Progress

Nephronophthisisiasis, Renal Transplant, at University

Treatment

Calcium Supplementation

Oral (calcium phosphate, calcium sandoz)

Intravenous (needs central access, ECG monitoring)

Vitamin D

Vitamin D supplementation ergocalciferol/ colecalciferol

(RCPCH guidelines 2016)

1, 25 dihydroxycolecalciferol/ alfacalcidol

(CKD stage 4/5)

Treatment

Dialysis

Tumour lysis

Rhabdomyolysis

ARF/CRF

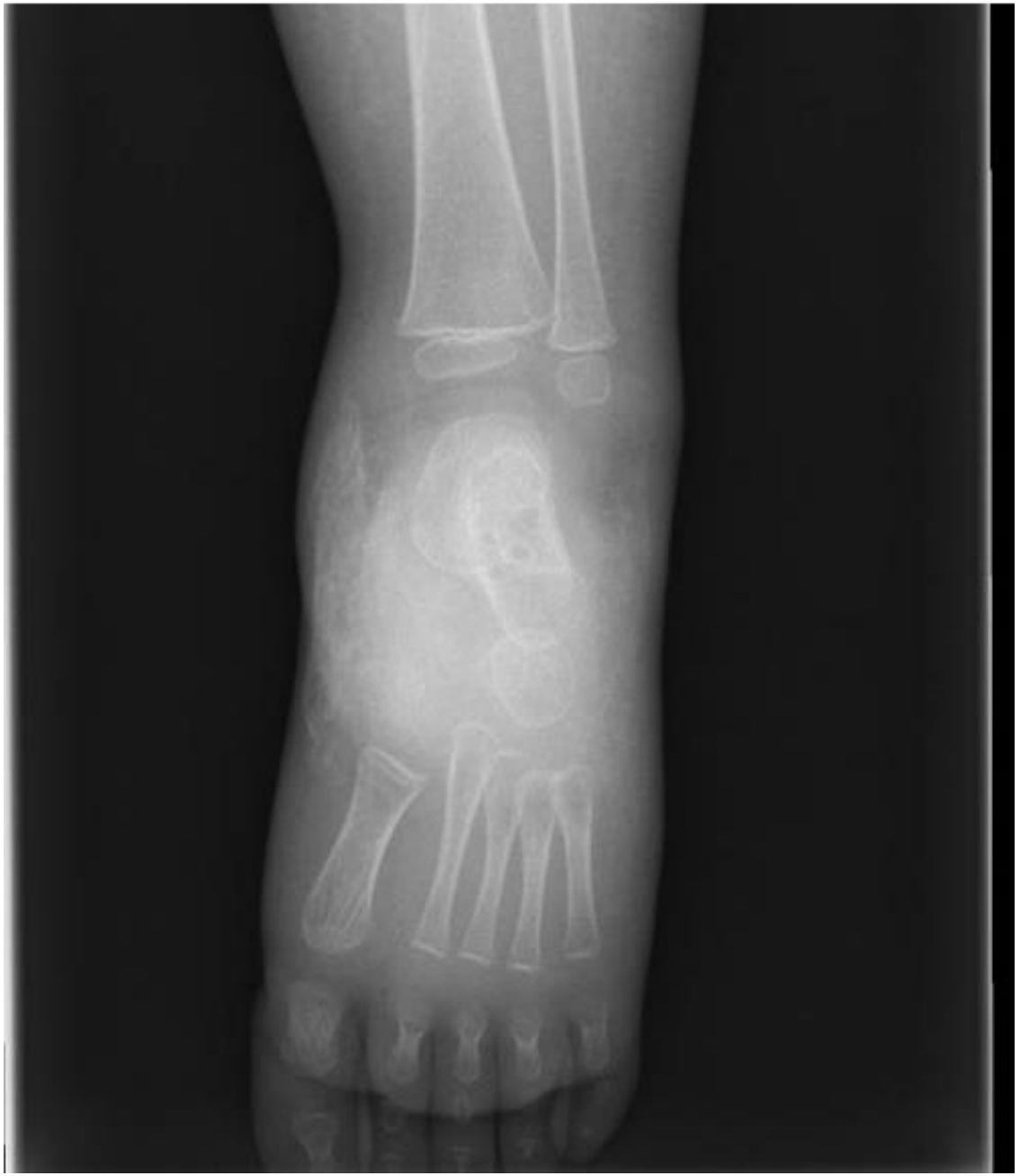
Acidosis in renal failure

Treat calcium before acidosis

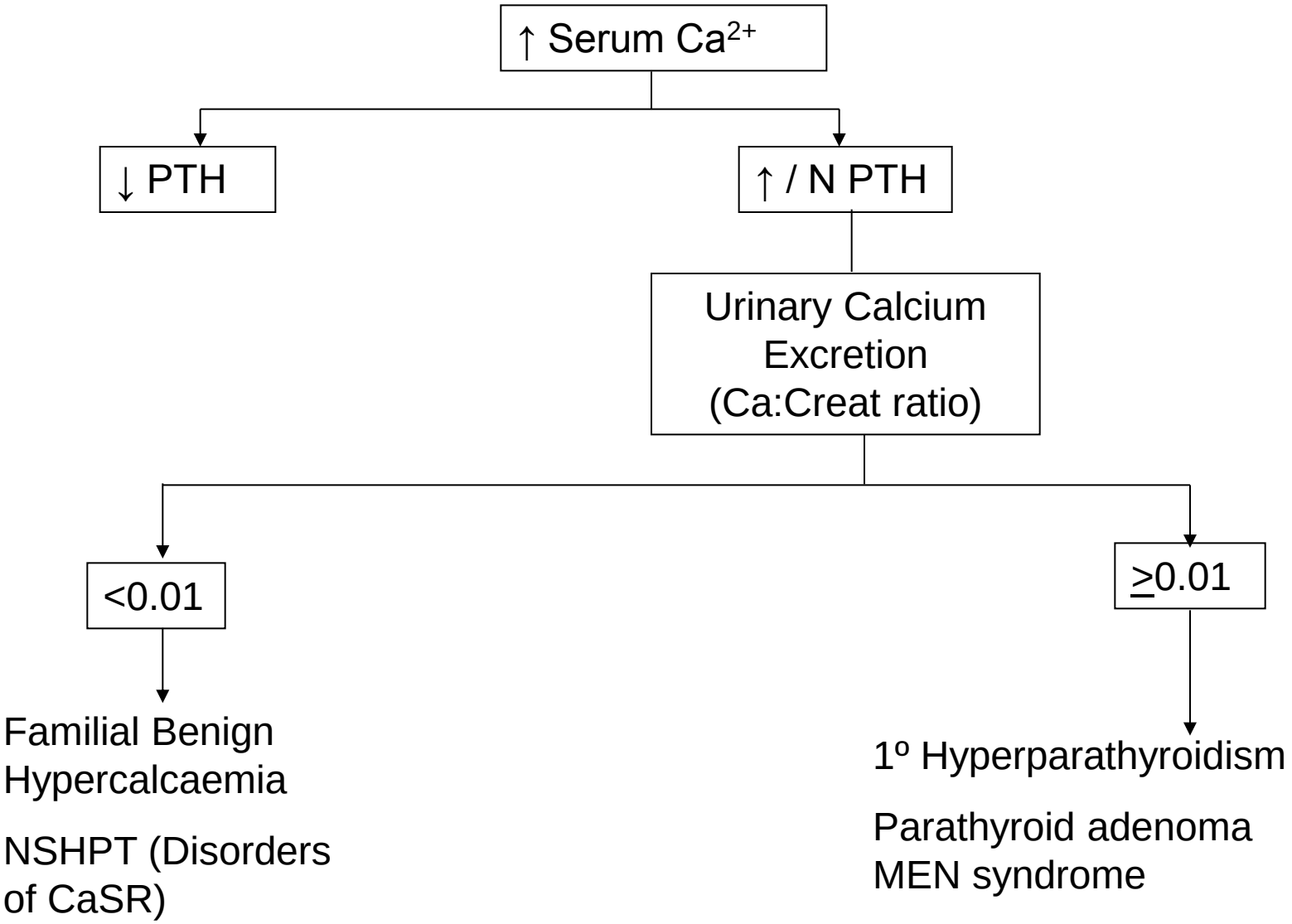
Magnesium supplements

Nephrotic syndrome

? Ionised calcium/ ? Diuretics



Hypercalcaemia (↑/N PTH)



CaSR MUTATIONS

Inactivating Mutations - FBHH

→ moderate resistance of parathyroid glands to Ca^{2+}

→ higher Ca^{2+} levels needed to achieve half maximal inhibition of PTH release

Mutation of same receptor in kidney → cannot upregulate Ca2+ excretion despite hypercalcaemia

→ hypocalciuria

HYPERCALCAEMIA WITH PARADOXICAL HYPOCALCIURIA (PTH high/normal)

M.E.N

- Commonest cause of familial hyperparathyroidism
- A.D
- 2 or more endocrine tumours in same person, multiple tumours in same tissue
- Hyperparathyroidism most frequent endocrinopathy in MEN 1

↑PTH in CRF

2ry Hyperparathyroidism ↑ PTH, ↑ PO_4, Ca ↔

Treatment

Increase Ca	Ca supplements (diet, dialysis)
	Vitamin D (colecalciferol, alfacalcidol, paracalcitol)
Reduce Phosphate	Diet (Diary , Phosphate binders)
	Dialysis

TRANSPLANT

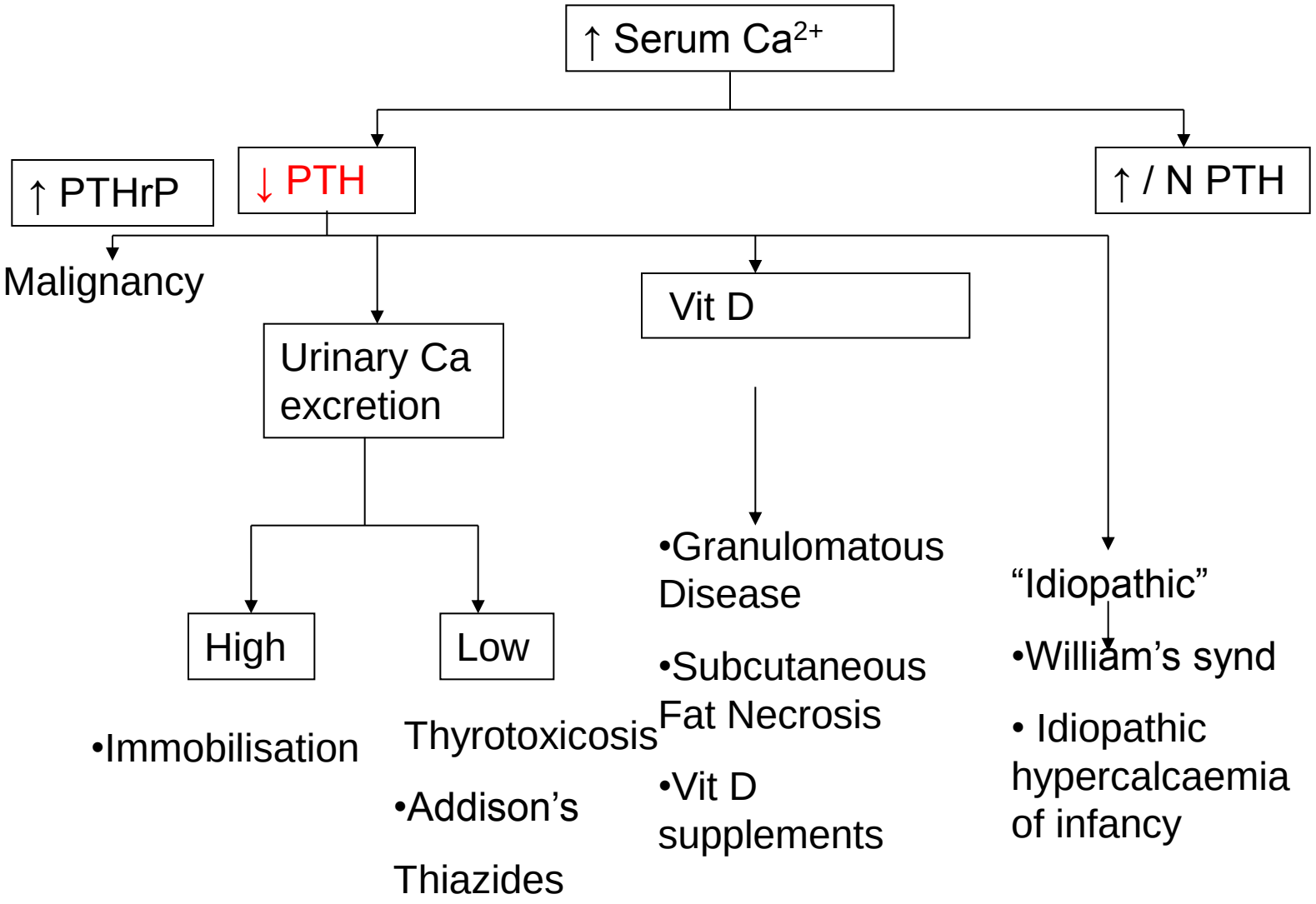
3ry Hyperparathyroidism ↑ PTH, ↑ PO_4, ↑ Ca

Treatment

Decrease Phosphate	Parathyroidectomy
Calciumimetics	

TRANSPLANT

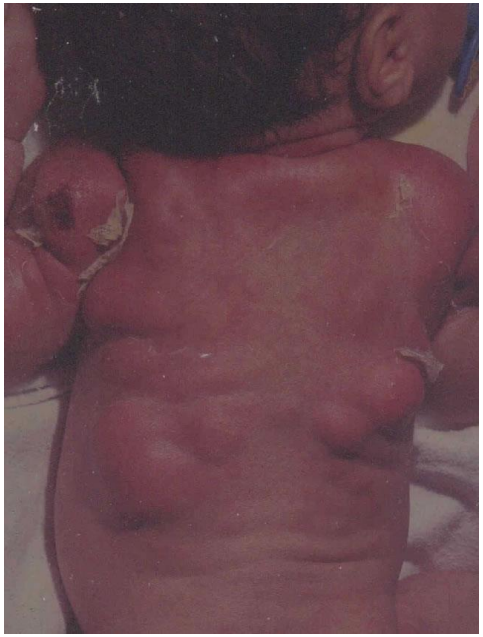
Hypercalcaemia (↓ PTH)



Hypercalcaemia (↓PTH)

Inappropriate activation of 1α-hydroxylase within macrophages

- Subcutaneous fat necrosis
- Sarcoidosis
- Other granulomatous disease
- Rx- steroids



Hypercalcaemia in CRF (↓PTH)

Cause	Overtreatment with Vit D analogs/ Ca supplementation
Biochemistry-	↓ PTH, ↑ Ca, ↔ PO_4
Risk	Adynamic bone disease
Treatment	Stop Vit D / Ca suplements

Clinical symptoms

BONES
STONES
ABDOMINAL GROANS (Constipation, polyuria , FTT, anorexia)

RENAL
Vasoconstriction, hypertension
Intravascular depletion

OTHER
headache, psychosis
Cardiac arrhythmia
Pancreatitis
Ectopic calcification

Treatment

Reduce calcium absorption	Low calcium intake (Locosol) Stop vitamin supplements
Increase calcium excretion	Normal saline + frusemide
Drive calcium into bone	Bisphosphonates (renal failure) Calcitonin
Steroids	Granulomatous lesions
Reduce PTH	Decrease phosphate (diet, dialysis, phosphate binders) Calciumimetics Parathyroidectomy (1ry and 3ry)

Clinical Case

Age 10, caucasian girl

General lethargy, thirst

Examination- Small, abdominal mass, hypertension

Biochemistry-	Cr 363µmol/l, urea 22mmol/l, K 4.4 mmol/l; Bicarb 16mmol/l Ca 3.5mmol/l, PO4 0.9mmol/l, Alb 45g/l; PTH 0.6pmol/l Vit D 23ng/ml
US	3 abdominal masses with calcification, mild hydronephrosis, partially filled bladder
DD	ovarian teratoma, small round cell tumour

Clinical case

Treatment	IV fluids with frusemide; low calcium diet ovarian dysgerminoma with mets Amlodipine
Day 5	Ca 2.5mmol/l and Cr 255µmol/l
Day 14	Surgery and commenced chemotherapy
2 years	creatinine reached a nadir of 73µmol/l
8 years	Creatinine 92µmol/l (eGFR 60), small echobright kidneys on Amlodipine , in remission