

Metabolic Bone Disease

BOA Instructional Course 2012

K Sherman FRCS, M.Ed, PhD

Learning Outcomes

At the end of this session you should:

- *Have an understanding of basic calcium and phosphate homeostasis and the interplay between Vitamin D and PTH in bone metabolism*
- *Be able to describe the underlying mechanisms of the most common abnormalities of bone metabolism encountered in Orthopaedics*

Scope of talk

- Calcium and phosphate regulation
- Vitamin D metabolism
- Effects of active Vitamin D
- Effects of PTH

- Osteomalacia
- Hyperparathyroidism
- Renal osteodystrophy
- Pagets disease
- Osteoporosis

Bone remodelling

- Bone is a **living** structure that is constantly undergoing repair and remodelling
- Remodelling takes place in Bone Structural Units (BSU), or remodelling units
- Normally resorption and formation are “**coupled**”
- Remodelling cycle:
 - Resorption
 - Reversal (cement line deposition)
 - Formation

Architectural remodelling

- Architectural plan put into action
 - Genetic control
- Project supervision
 - Hormonal control
- Demolition/Construction workers
 - Osteoclasts/Osteoblasts
- Materials
 - Calcium & Phosphate
- Infrastructure (roads, recycling plant)
 - Vascular supply, kidney etc.

The plan and how it is put into action

- Osteoblast differentiation requires Runx-2 transcription factor (single gene) and also Osterix transcription factor etc.
- Wnt signalling pathway works partly through stimulation of Runx-2 gene expression
- Wnt pathway probably involved in the action of PTH

Bone Remodelling

- **Osteoblasts** are of mesenchymal stem cell origin – a few become “entombed” in bone become osteocytes, the others become lining cells or apoptose
- **Osteoclasts** derived from granulocyte/macrophage-forming colony units (CFU-GM)

Bone Remodelling

- Osteoclast differentiation probably requires cell to cell contact with osteoblasts and also Macrophage Colony Stimulating Factor (M-CSF)
- RANKL/RANK interaction activates osteoclast formation
- RANKL/RANK interaction blocked by Osteoprotegerin (Osteoclastogenesis Inhibitory factor)
- RANKL also binds with Osteoprotegerin

Metabolic bone disease

- Often involves a loss of regulation of the tight coupling between bone resorption and formation
 - Excessive resorption in Hyperparathyroidism and Pagets
 - Impaired resorption in Osteopetrosis

Bone disease

- Bone is the major source of calcium in the body (99%)
- Calcium is essential for cell function
- Some bone disease occurs because bone formation and remodelling may not take priority if the materials are required more urgently elsewhere (e.g. muscle contraction & coagulation)

The normal regulation of calcium and bone formation

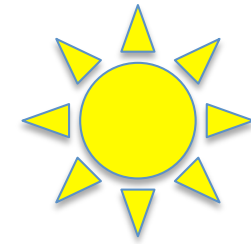
Two hormones are largely responsible for the regulation of calcium and phosphate and the supply of calcium and phosphate for bone formation:

- Active form of Vitamin D
(1,25-Dihydrocholecalciferol - Calcitriol)
- Parathyroid hormone (PTH)

Vitamin D metabolism

Ergosterol (Vit D₂) in **food**

7 – dehydrocholesterol in **skin**



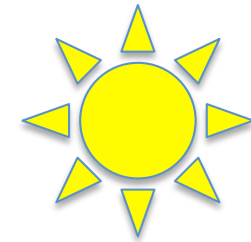
Cholecalciferol (Vit D₃)

- Vitamin D = fat soluble
- Vitamin D₂ absorbed from intestine by incorporation in micelles and then packaged in chylomicrons
- Vit D₃ bound to Vit D binding proteins and then transported in the blood

Vitamin D metabolism

Ergosterol (Vit D₂) in **food**

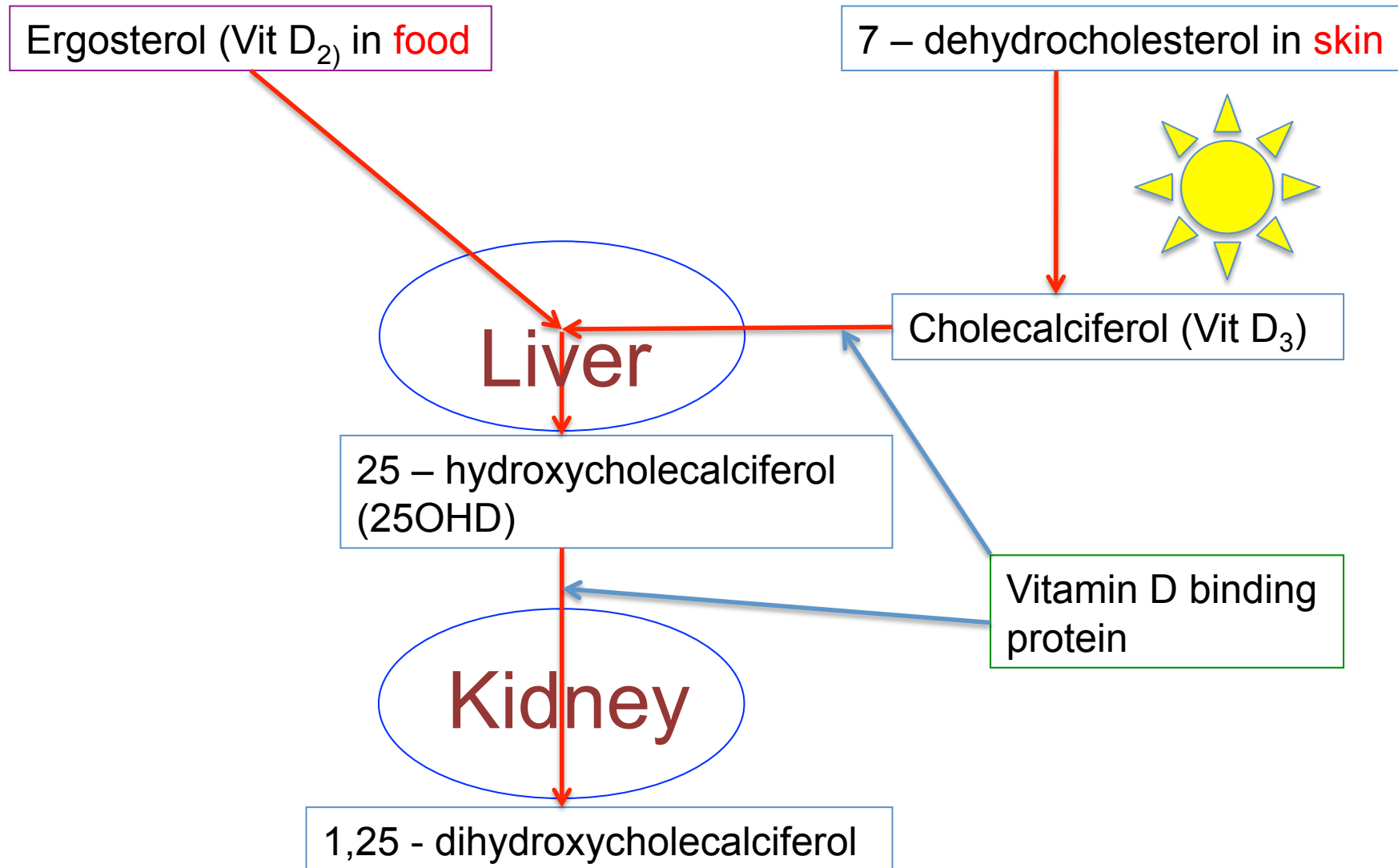
7 – dehydrocholesterol in **skin**



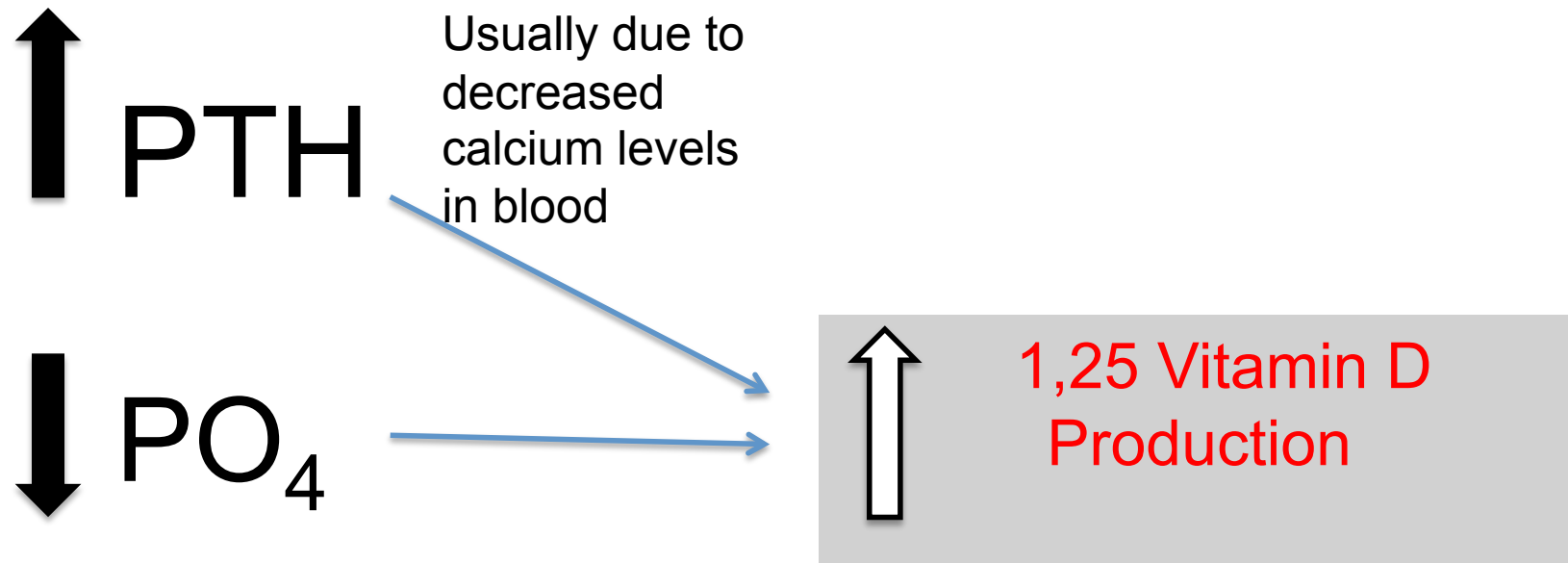
Cholecalciferol (Vit D₃)

- Vitamin D undergoes two hydroxylations to become the active form 1,25-dihydroxycholecalciferol
- The inactive form 24,25-dihydroxycholecalciferol can be formed

Vitamin D metabolism



Vitamin D in the kidney



Vitamin D released from binding proteins in tubular cells and hydroxylated to active or inactive form.

What does active Vitamin D do?

- Increases intestinal absorption of calcium
- Increases intestinal absorption of phosphate
- Decreases calcium excretion in kidney
- Suppresses PTH production
- Regulates osteoblast function
- Facilitates PTH induced osteoclast activation

Direct actions on
intestine, kidney and
bone

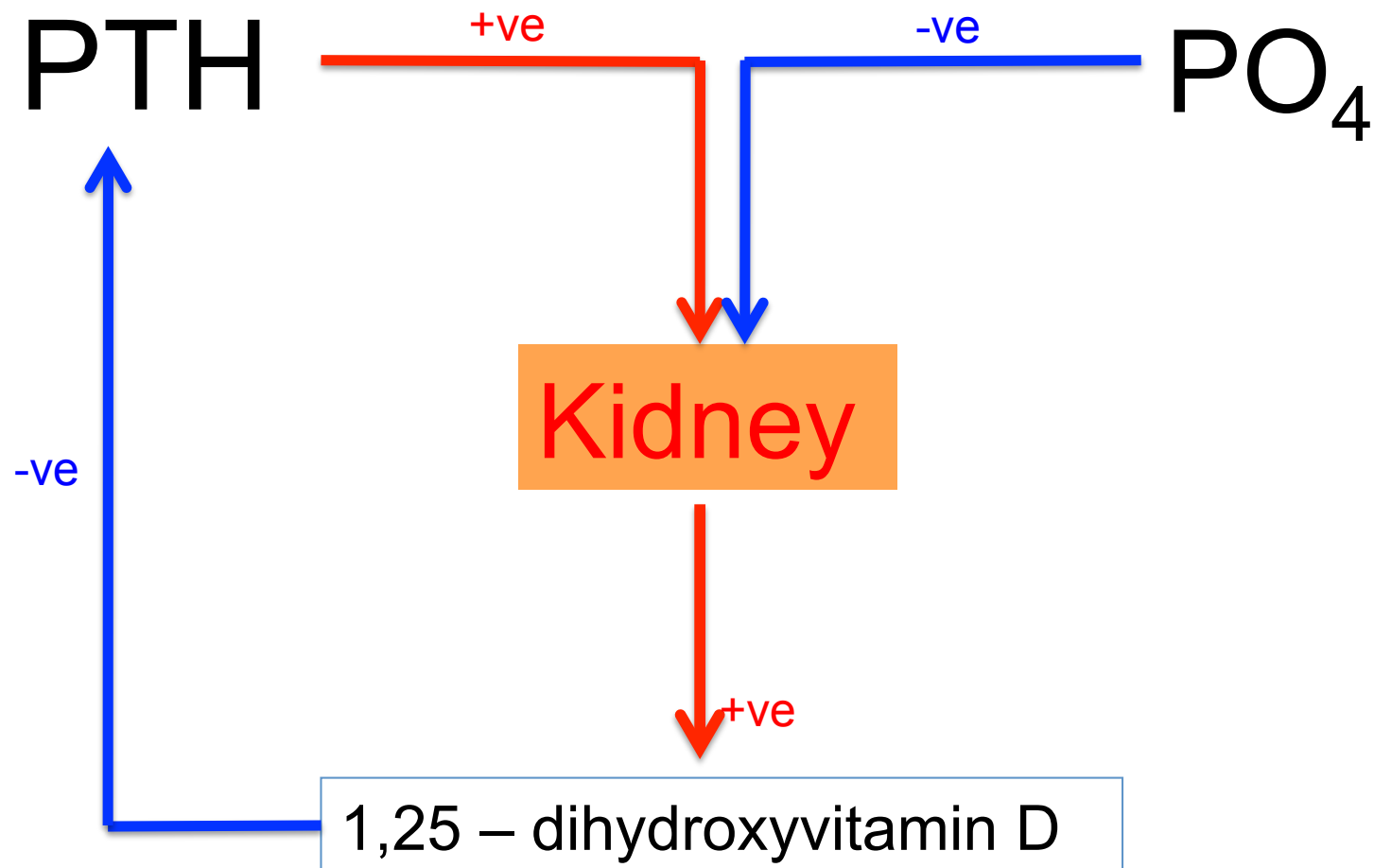
Net effects of Vitamin D

- Increases Calcium levels in blood
- Increases PO_4 levels in blood
- Aids bone formation
- BUT in high doses if deficiency of Calcium and Phosphate it can cause bone resorption

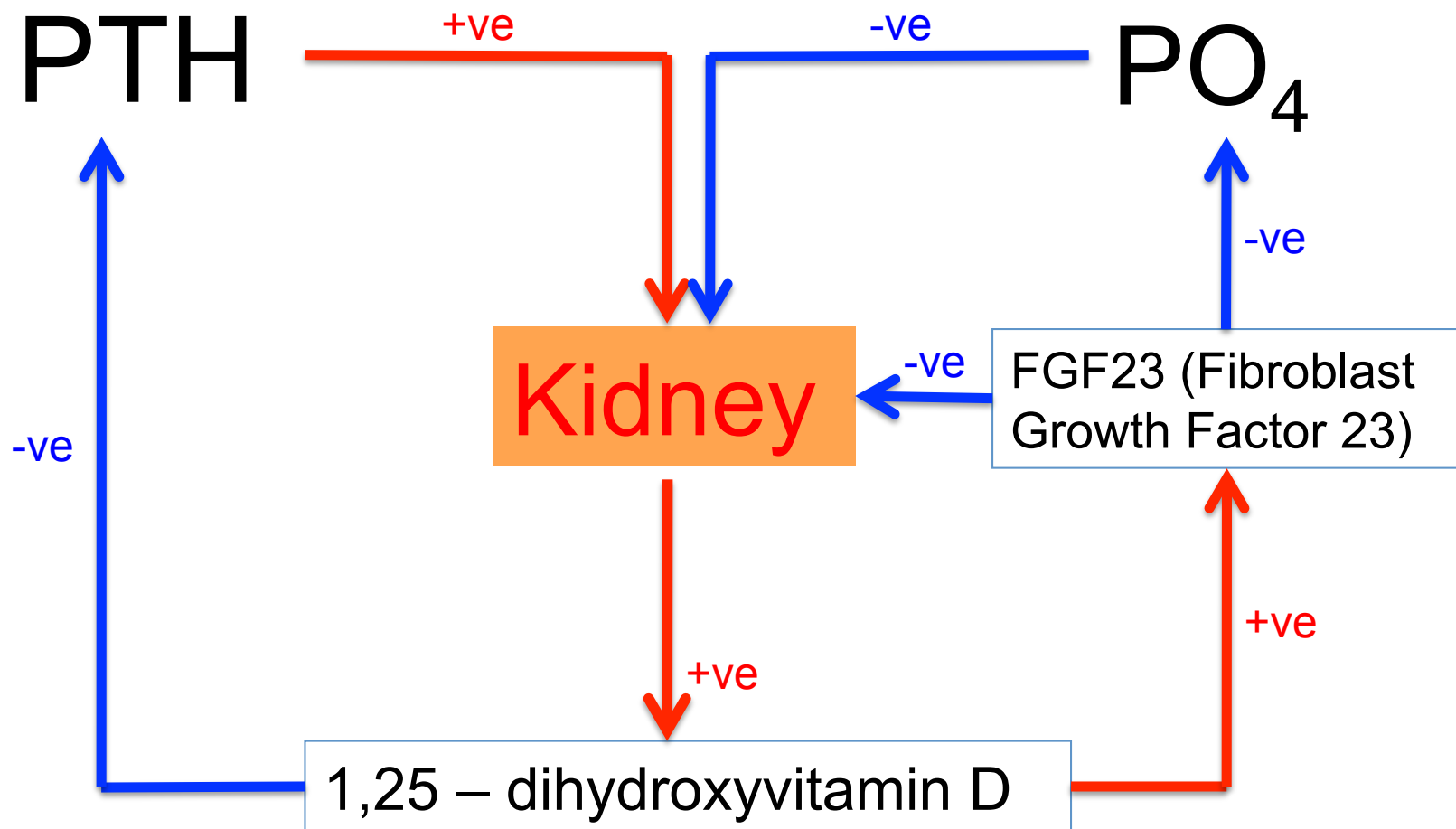
Vitamin D deficiency

- Early
 - phosphate levels low
- Later
 - calcium levels also low
 - Secondary hyperparathyroidism – phosphaturia, demineralisation of bone and osteomalacia

How is Vitamin D regulated?

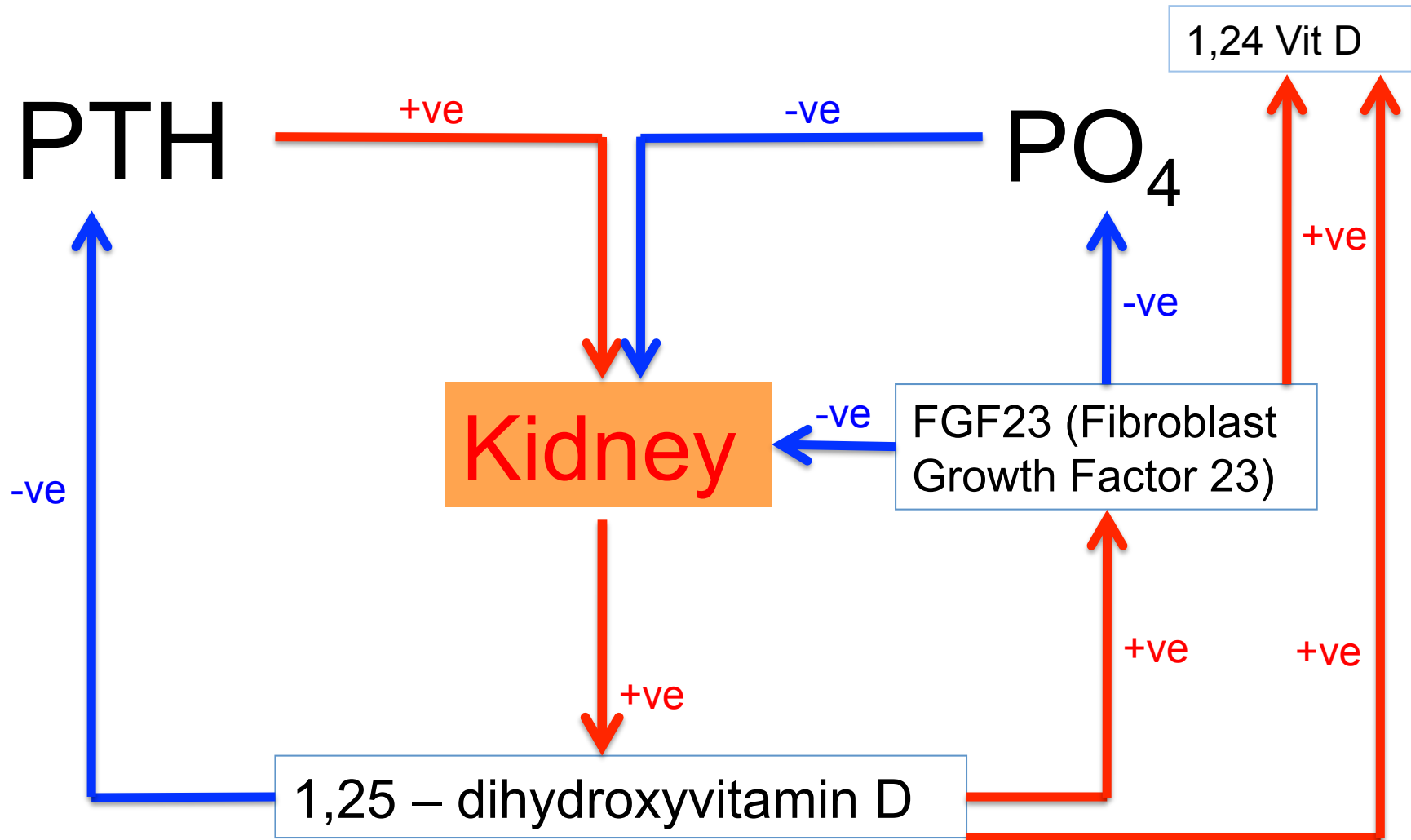


How is Vitamin D regulated?



Increased Phosphate due to FGF23 balanced by increased Phosphate absorption due to 1,25 Vit D

How is Vitamin D regulated?



Increased Phosphate due to FGF23 balanced by increased Phosphate absorption due to 1,25 Vit D

PTH

- PTH is the primary regulator of serum calcium levels
- Synthesized by cleavage of pre-pro-PTH 115-amino acid polypeptide to PTH 1-84
- Half life of PTH 1-84 is 2 – 4 minutes
- If not required degraded to inactive forms
- PTH and 1,25 Vitamin D regulation is closely inter-related.

Parathyroid Hormone actions

Serum Calcium

- Increases renal reabsorption
- Releases calcium from skeletal stores
- Increases bone resorption
- These effects all increase the serum calcium level

Phosphate

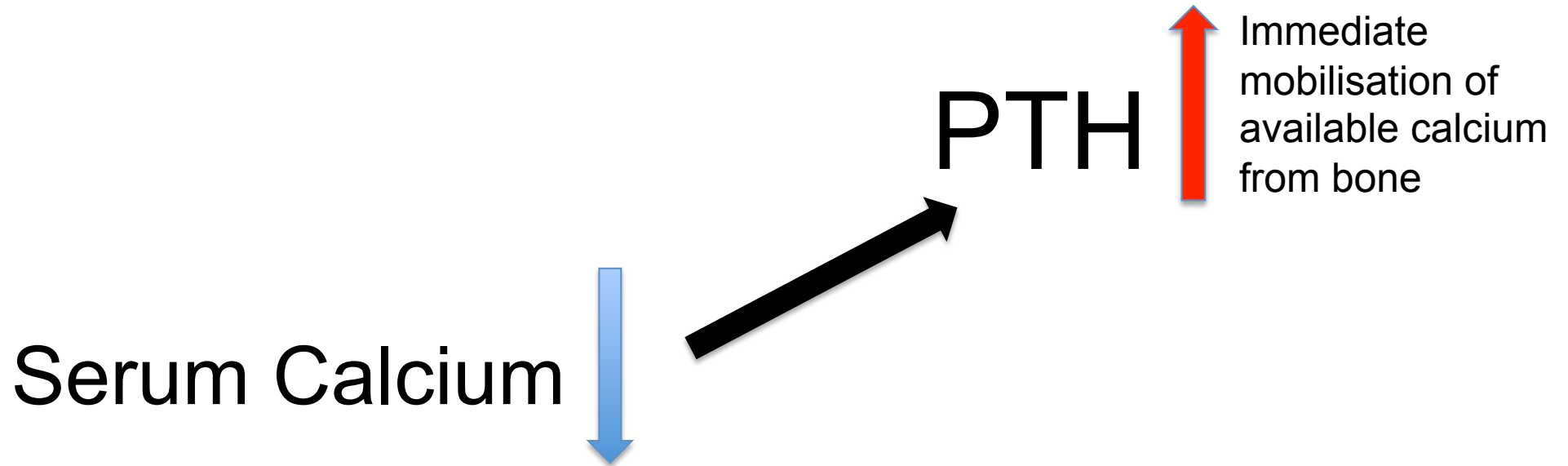
- Decreases renal reabsorption
- Increases bone resorption
- These effects can balance out

Main actions on kidney and bone

Net effect of PTH

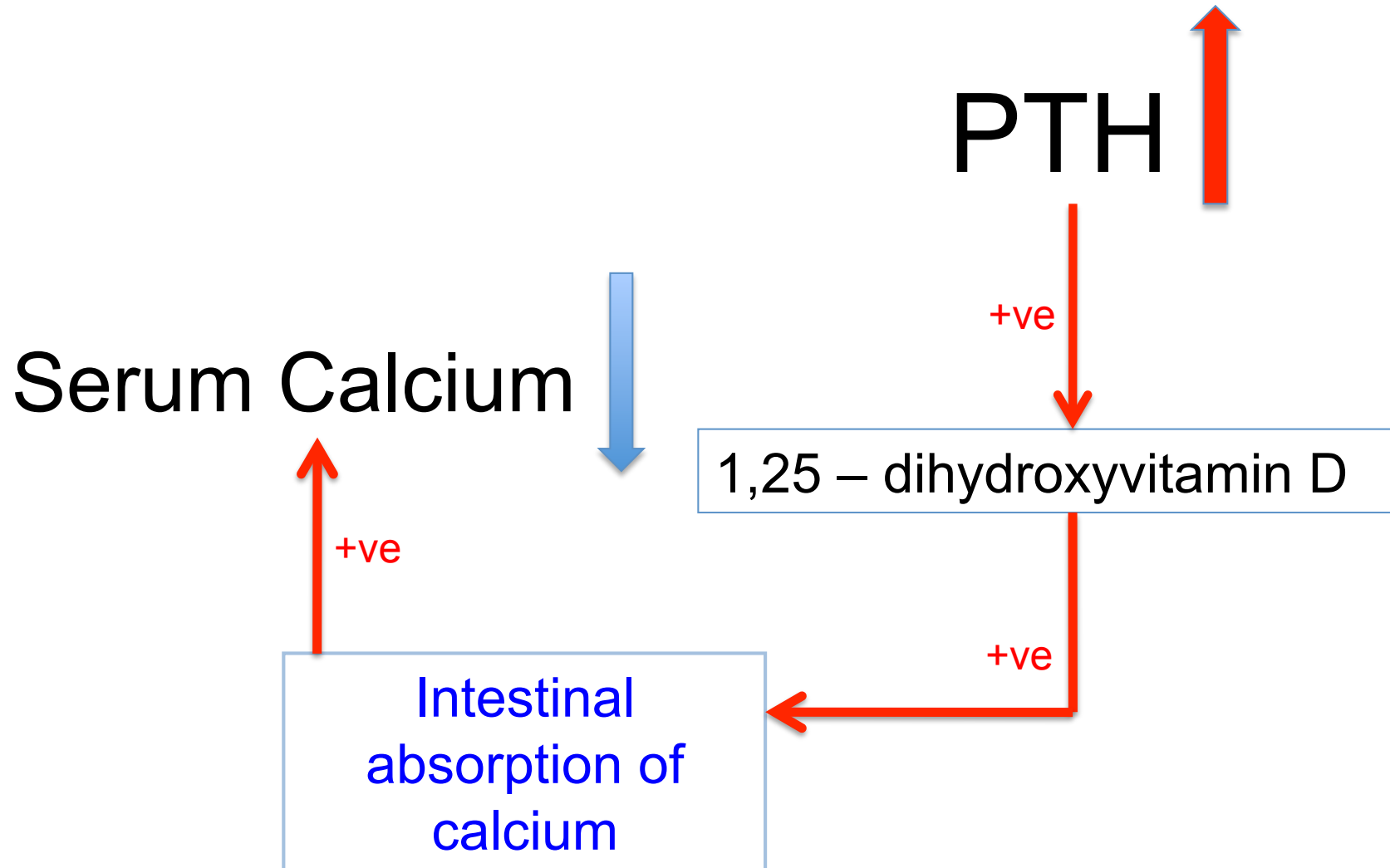
- Increases serum Calcium levels
- Bone resorption – if in chronic continuous excess causes
 - Mainly through effect on RANKL & Oteoprotegerin
- Bone anabolism - if given intermittently causes

Calcium regulation

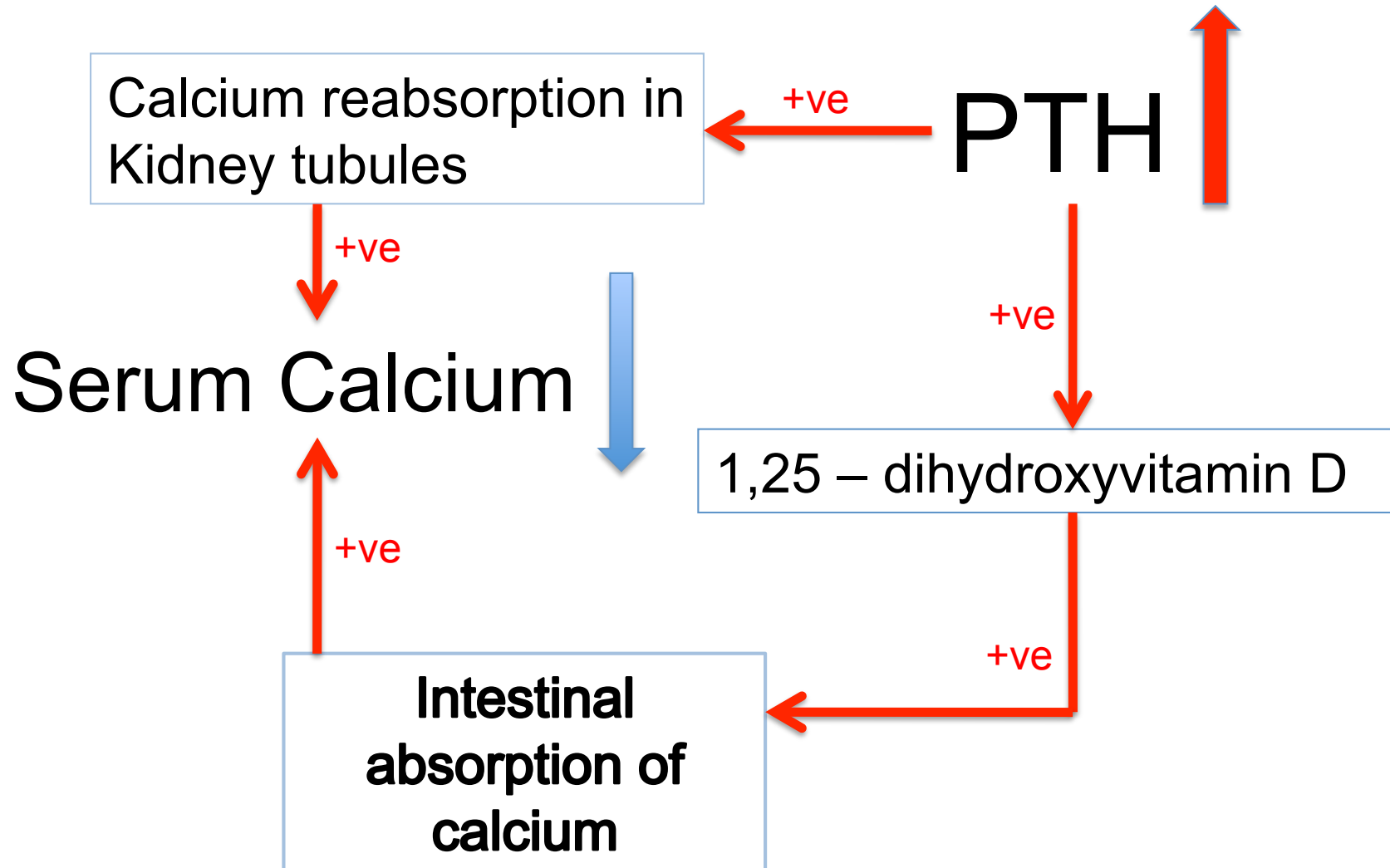


1. Seconds to Minutes – PTH secreted
2. Minutes to first hour – Active PTH degradation in parathyroid cells decreased
3. Hours to days – increased PTH gene expression
4. Days to weeks – parathyroid cells increase in numbers

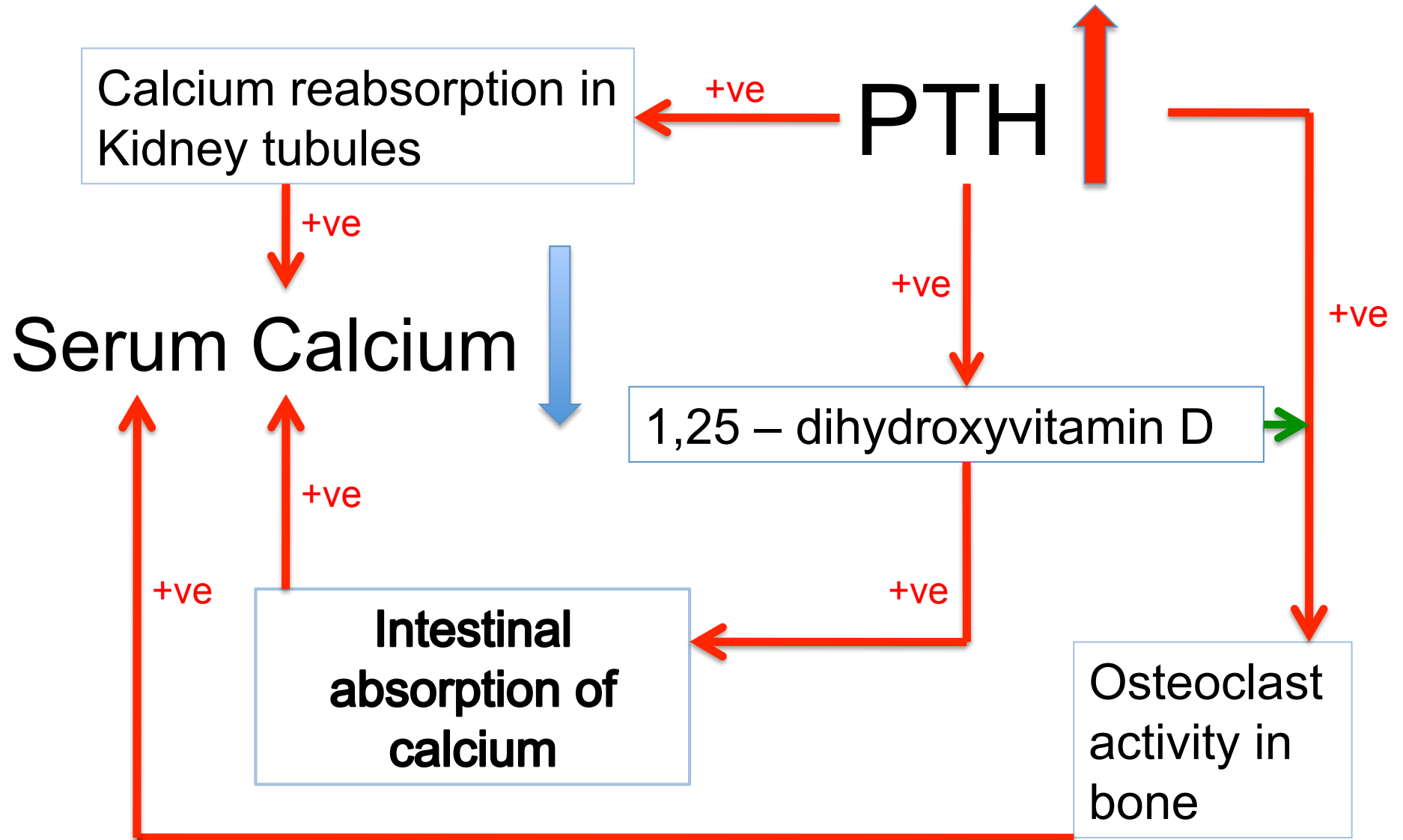
Calcium regulation



Calcium regulation



Calcium regulation



Bone diseases

Osteomalacia and Ricketts

May be caused by:

- Insufficient active Vitamin D metabolite
- Inadequate phosphate

Osteomalacia

- Diagnosis

- Clinical

- Bone pain and tenderness
 - Proximal muscle weakness
 - Fracture (incomplete or bilateral)
 - Muscle spasms and cramps

- Blood tests depend on cause

- Tetracycline labelled bone biopsy best (also needed to detect aluminium deposition)

Osteomalacia & Rickets

Causes:

- “Failure of supply” – insufficient “raw materials”
 - Inadequate formation in skin
 - Nutritional deficiency (usually Vit D)
 - Failure to absorb in gut
- “Processing problems” – affect processing of raw materials
 - Problems with synthesis or activity of 1,25 D H Cholecalciferol
Including renal failure
 - Autosomal dominant Hypophosphataemic Rickets (FGF23 degradation fault)
- “Recycling” problems” – affect preservation/cycling of essential ingredients
 - X-linked Hypophosphataemic Vitamin D resistant rickets/osteomalacia
 - Renal tubular acidosis
 - Renal failure – glomerular, and misc causes

“Intake problems”

Failure of supply

- Lack of sunlight (or patients with extensive burns)
- Vit D deficiency in diet
- Ca chelators – e.g. Oxalates
- Phosphorus - e.g. aluminium antacids

GI Absorption defects

- Biliary disease – steatorrhea (interferes with fat soluble Vit D)
- Short bowel syndrome/gastric bypass etc
- Crohns and Coeliac disease

”Processing problems”

Vitamin D Resistant Rickets

- Type I – Genetic or acquired deficiency of enzyme converting 25 D H Cholecalciferol to 1,25 D H Cholecalciferol
- Type II – organ insensitivity to 1,25 D H Cholecalciferol (Autosomal recessive – very rare)

Medication

- Enzyme induction converts 25 Vit D to inactive metabolites (phenytoin, phenobarbitone, rifampicin etc.)

“Processing Problems”

- **Renal failure** – tubular cell damage preventing 1,25 hydroxylation
- **Hypophosphatasia**
 - Defective phosphate synthesis
 - Autosomal recessive
 - Increased urinary phosphethanolamine
- **Autosomal dominant hypophosphataemic rickets**
 - Impaired degradation of FGF23

“Recycling problems”

Renal Tubular Defects (phosphate leak)

- X-linked hypophosphataemic Vitamin D resistant rickets/osteomalacia
- Albrights syndrome
- Fanconi syndrome – several types
- Phosphaturia and glycosuria +/- aminoaciduria

Renal Tubular Acidosis

- Acquired (systemic disease)
- Genetic
 - Debre-De-Toni-Fanconi syndrome
 - Lignac-Fanconi syndrome
 - Lowe’s syndrome

Osteomalacia

- **Most common causes:**
 - Chronic renal failure
 - Vitamin D deficiency
 - Vitamin D pathway abnormalities
 - Hypophosphataemic syndromes
- **Rarer causes:**
 - Renal tubular acidosis
 - Aluminium toxicity
 - Hypophosphatasia
 - Mesenchymal tumours causing hypophosphataemia

Osteomalacia – blood parameters

Vitamin deficiency

- Low phosphate
- Very low 25 OHD
- Raised alkaline phosphatase
- Normal or low calcium

Phosphate losing conditions

- Low phosphate
- Normal 25 OHD
- Normal alkaline phosphatase
- Normal calcium

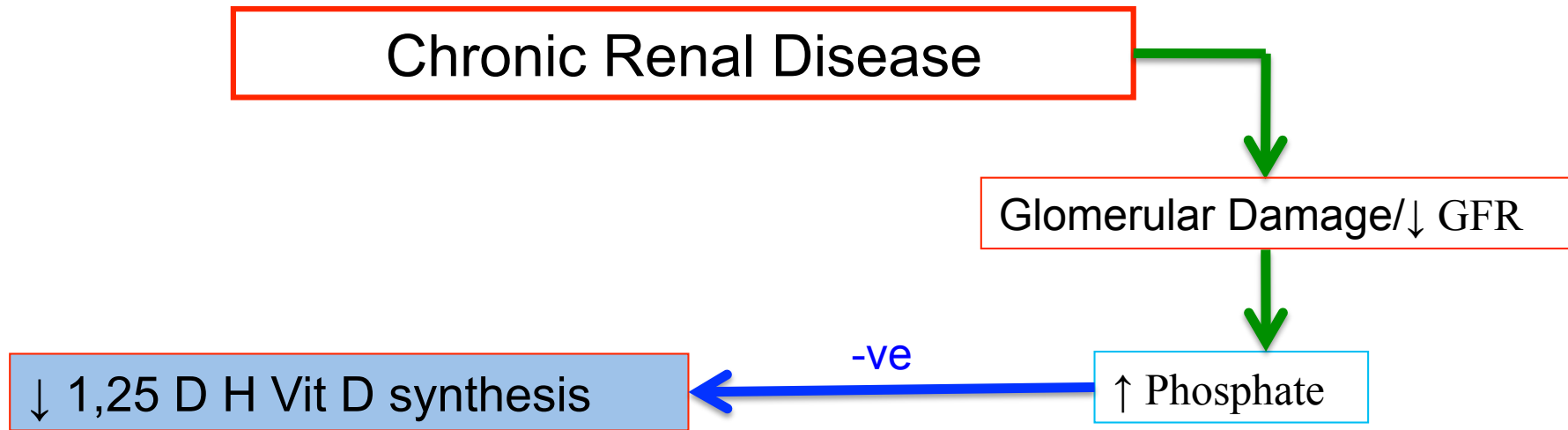
Treatment of osteomalacia

- Aim is to restore serum calcium and phosphate levels to normal
 - In Vit D deficiency states replace Vitamin D or metabolite distal to any block
 - In Vit D resistant conditions must replace both Phosphate and 1,25 D H Cholecalciferol (to suppress PTH)

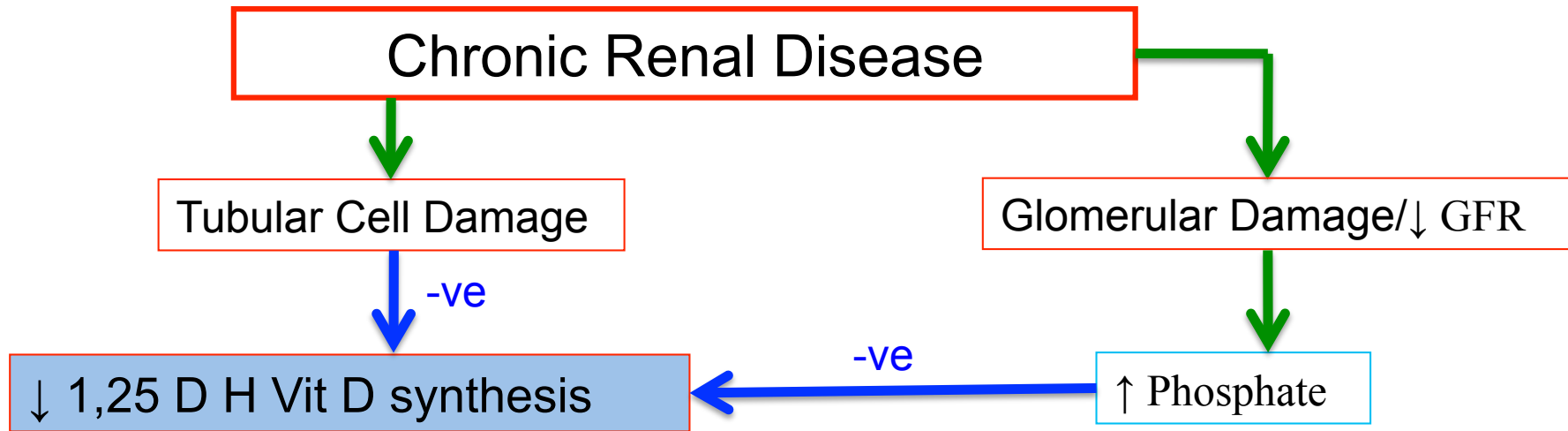
Renal Osteodystrophy

- Common in renal failure
 - Uraemia causes **phosphate retention**
 - Failure of 1,25 D H Vit D formation **in renal tubules**
 - Acidosis (if GFR < 20 mls/min) causes further failure of **calcium retention**
- Can result in:
 - **Rickets or osteomalacia** (partly due to ↑ aluminium)
 - **Osteoporosis**
 - **Secondary hyperparathyroidism** causes ↑ Ca
 - Calcification (due to high calcium levels)
 - Osteitis fibrosa cystica (increased bone resorption)
 - **Osteosclerosis (20%)**

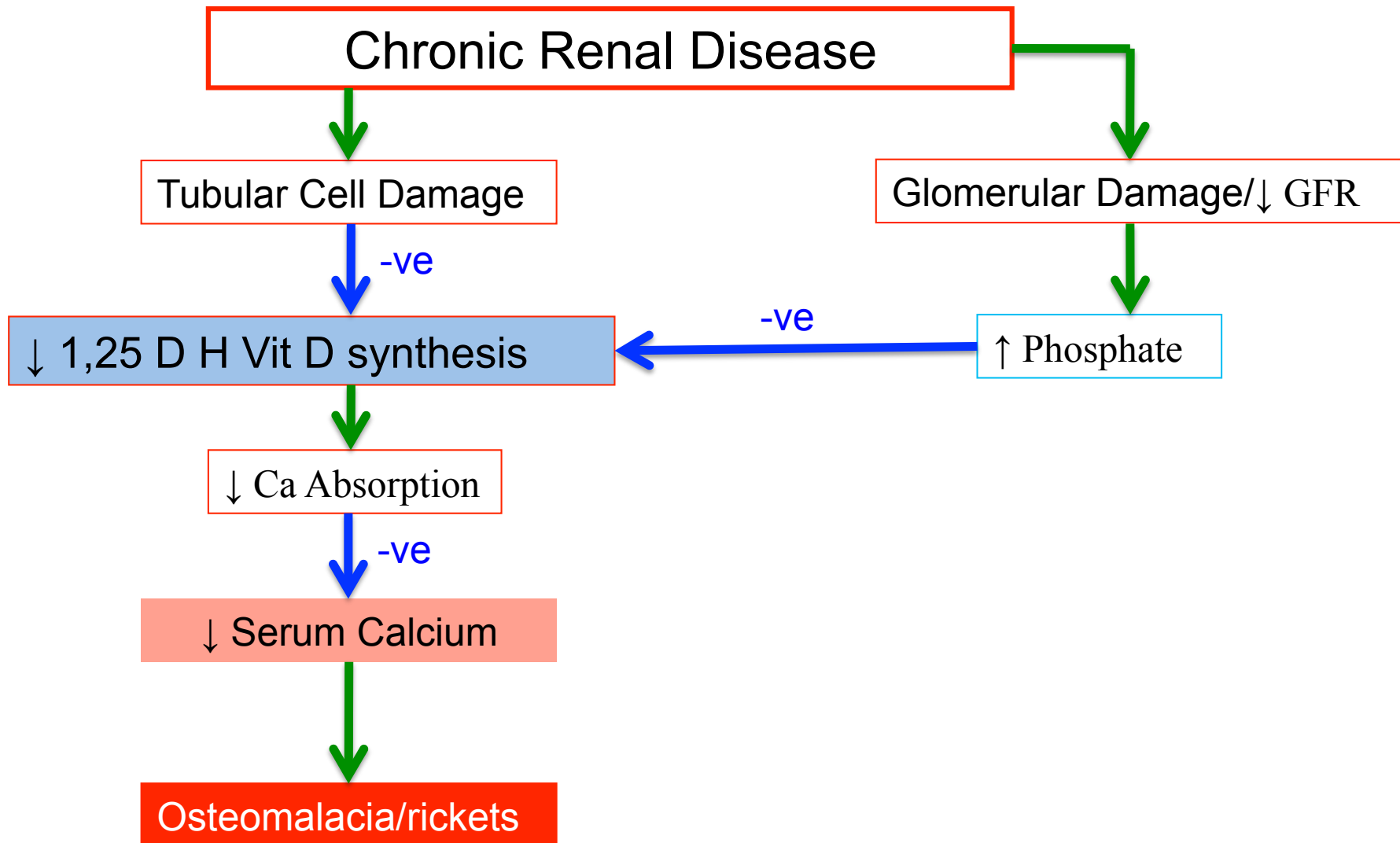
Renal disease



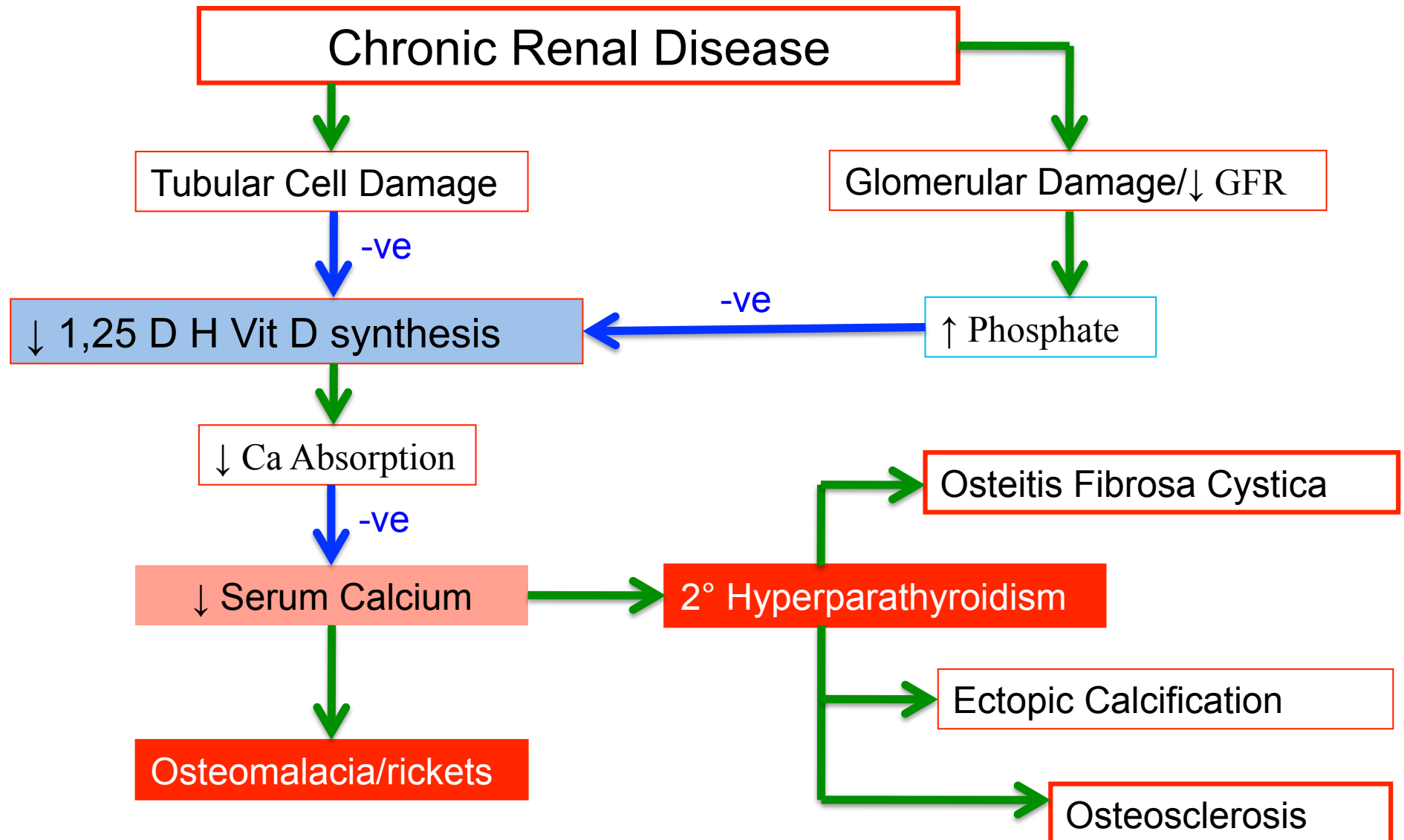
Renal disease



Renal disease



Renal disease



Renal Osteodystrophy

High Bone Turnover

- Phosphate retention
 - Reduced 1,25 D H Cholecalciferol
- High PTH (Secondary hyperparathyroidism)
 - Osteitis Fibrosa cystica
 - Osteosclerosis
 - Soft tissue calcification

Low Bone Turnover

- Aluminium deposition
 - PTH release inhibited
- Low PTH
- Osteomalacia

But pattern of Calcium and bone changes is complex

Renal Osteodystrophy

- Treatment:
- Decrease phosphate
 - Diet
 - Calcium carbonate to bind phosphate
- Increase Calcium
 - Diet
 - 1,25 D H Cholecalciferol

Where indicated chelate aluminium

Osteoporosis

Characterised by:

Low bone mass per unit volume

Osteoporosis

WHO consensus definition states that osteoporosis is a systemic skeletal disease characterised by low bone mass, micro-architectural deterioration of bone tissue leading to enhanced bone fragility and a consequent increase in fracture risk.

Osteoporosis

■ How is the bone mineral density measured?

DEXA scan

■ What does DEXA stand for?

Dual Energy X-ray Absorptiometry

■ Why does the scan use dual energy?

To minimize the effect of fat

Osteoporosis

Definition?

- 2.5 S.D. below?
- Mean for young adults
- What is a T-score?
- Sex and race matched mean for young adult
- What is a Z-score
- Age sex and race matched mean
- What is the use of a Z-score?
- A low score indicates a cause other than age-related loss of bone mineral

Osteoporosis

Primary Osteoporosis

Secondary Osteoporosis

Osteoporosis (Riggs & Melton)

- **Type I:**
 - Related to loss of oestrogen at the menopause
 - Affects mainly cancellous bone at the time of menopause so vertebral and distal radial fractures are common
 - High turnover osteoporosis
- **Type II:**
 - age-related and
 - affects cortical and cancellous bone;
 - occurs 10 – 15 years later than type I
 - poor calcium absorption
 - low turnover osteoporosis

Osteoporosis

Treatment and prevention of complications?

Osteoporosis treatment

- Exercise
- Calcium & Vitamin D
 - Minimizes bone resorption
 - Best for type II
- Oestrogen (HRT)/Oestrogen receptor modulators, e.g. Raloxifene – within a few yrs of menopause
 - Inhibits effect of PTH on Osteoclasts
 - Type I
- Bisphosphonates
 - Inhibit osteoclasts
- Recombinant PTH
 - Stimulates bone formation – activates bone lining cells and osteoblasts

Pagets disease

3% over 40 yrs

15% - 25% familial

15% monostotic, 85% polyostotic

Rare in Scandinavia, more common in
UK, USA, Australia, NZ, Germany

Pagets disease

- 3 phases
 1. Osteoclastic activity (“Lytic”) – usually in metaphysis or in skull)
 2. Osteoblastic/osteoclastic activity (“Active”)
 3. Inactive (“Burnt out”) – sclerotic
- Biopsy shows multiple resorbing lacunae
- Blood tests show ↑ bone Alk Phos & ↑ urinary hydroxyproline

Pagets – problems for Orthopaedic Surgeons

- Bleeding from bone following surgery
- Variable texture of bone
- Compression of vital structures (e.g. in spine)
- Deformity
- Hypercalcaemia on immobilisation
- Cardiac problems

Pagets Treatment

- Nitrogen-containing **Bisphosphonates**
 - IV - Zoledronic acid, Pamidronate
 - Oral – Risedronate, Alendronate
- Intravenous more effective and longer lasting
- Orals poorly absorbed
- Need to treat for three months pre-op
- Complications
 - Hypocalcaemia – give Vit D & Calcium
 - Musculoskeletal pain (may be delayed)
 - Osteonecrosis of jaw