Disorders of Calcium, Phosphate and Magnesium Homeostasis

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Disorders of Calcium Homeostasis
## Disorders of Calcium Homeostasis

### Outline

- **Brief revision of calcium physiology**
- **Definitions**
  - Osteomalacia and rickets
    - Contrast to osteoporosis
  - Hypocalcaemia and hypercalcaemia
- **Causes and consequences**
  - Vitamin D deficiency
  - Hypocalcaemia
  - Hypercalcaemia
- **Illustrative cases**
Summary of Calcium Homeostasis
Response to a Decrease in Serum Calcium

- sCa$^{2+}$ increases PTH
- PTH increases u-phos
- u-phos increases s-phos
- s-phos increases 1,25-(OH)$_2$ vit D
- 1,25-(OH)$_2$ vit D increases Ca$^{2+}$ Absorption
- Ca$^{2+}$ Absorption increases Ca$^{2+}$ Reabsorption
- Bone Resorption increases

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Osteomalacia

- Impaired mineralisation resulting in softening of bone
  - There is accumulation of unmineralised osteoid
- The softened bone may deform and develop painful pseudofractures

Osteoid (unmineralised bone) is red
Mineralised bone is green
Rickets

- **Rickets**
  - Osteomalacia in a child
  - Growth plate is widened, cupped and frayed

Radiographs from Sir Edward Mellanby, first Professor of Pharmacology in Sheffield, and discoverer of the effect of cod liver oil in healing rickets
A case of rickets

- A girl presented age 2 yr 9 mo in 1932
- Seen by Professor Mellanby and treated with vitamin D3 (calciferol) 1500 IU/day
- Within 6 weeks the rickets appears to be healing
Rickets

Children living in the slums of Vienna, 1930’s

Radiographs of child’s legs
Showing bowing or genu varum
Are Osteomalacia and Osteoporosis the Same?
No!

• **Osteomalacia**
  – The bone is under-mineralised
  – There may be too little bone, but not always
  – This results in softening of the bone and the development of pseudo-fractures
    • These are not fractures as the apparent gap is filled with osteoid

• **Osteoporosis**
  – The bone is normally mineralised
  – There is too little bone
  – This results in fractures of the spine, wrist and hip
  – Pseudo-fractures never occur

Osteoid (unmineralised bone) is red
Mineralised bone is green

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Causes of vitamin D Deficiency

- Housebound
- Immigrants from the Indian sub-continent (‘Asian Rickets’)
- Malabsorption syndrome
- Anticonvulsant therapy, e.g. phenytoin
- Renal failure
- Lots of rare causes
VITAMIN D
Biosynthesis

Skin

Intestine

Liver

Kidney

Intestine

Bone

7-Dehydrocholesterol

UV - B

Vitamin D

25 - hydroxylase

25 - OH vitamin D

24 - hydroxylase

24,25 (OH)₂vit D

1α - hydroxylase

1,25 (OH)₂vit D

1,24,25 (OH)₃vit D

Calcitroic Acid

↑PTH

↓phos

↓Ca²⁺
How Does Vitamin D Deficiency Develop?

- **Housebound**
  - Lack of exposure to ultraviolet B light
- **Immigrants**
  - Lack of exposure to ultraviolet B light (dark skin, clothes)
  - Other factors
- **Malabsorption syndrome**
  - Malabsorption of dietary vitamin D
  - Loss of vitamin D in the faeces due to interruption of the enterohepatic circulation
- **Anti-convulsant therapy**
  - Accelerated breakdown (catabolism) of vitamin D in the liver
- **Renal failure**
  - Lack of conversion of 25-OHD to the active form, 1,25-(OH)₂D
What are the Consequences of Vitamin D Deficiency?

- **Hypocalcaemia**
  - Tetany

- **Osteomalacia**
  - Bone deformity and pain

- **Rickets**
  - Short stature, bone deformity and pain

- **Muscle weakness**
  - Proximal myopathy

- **Low serum vitamin D**
- **Poor calcium absorption**
- **Low serum calcium**
- **High serum parathyroid hormone**
- **Low serum phosphate**
  - The low calcium-phosphate product is the cause of the impaired mineralisation
- **High alkaline phosphatase reflects poor mineralisation**

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Case of osteomalacia

- Woman presented to A&E with overdose of anti-convulant therapy
- Pain too severe to tolerate
- Unable to stand

- Low vitamin D, serum calcium, phosphate, and high PTH and alkaline phosphatase
- No pain or weakness within 3 months of starting high dose vitamin D and calcium
- X-rays of hands (and feet) showed pseudo-fractures
Causes of Hypocalcaemia
Osteomalacia

The increase in PTH results from the decreased serum calcium and so is called ‘Secondary Hyperparathyroidism’

The low calcium-phosphate product is the cause of the impaired mineralisation
Causes of Hypocalcaemia
Hypoparathyroidism

Note – the mineralisation is normal as the calcium-phosphate product is normal –
The serum calcium may be low, but the serum phosphate is high
Note – the most common cause of decreased PTH is surgical damage to the parathyroids, although the condition can be idiopathic or genetic
Consequences of Hypocalcaemia

• **Muscle spasm**
  - Hands and feet
  - Larynx
  - Premature labour

• **Epilepsy**

• **Basal ganglion calcification**

• **Cataracts**

• **ECG abnormalities**
  - Long QT interval

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**Chvostek’s Sign**
Tap over the facial nerve
Look for spasm of facial muscles

**Trousseau’s Sign**
Inflate the blood pressure cuff to 20 mm Hg above systolic for 5 minutes

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Definition of Hypocalcaemia and Hypercalcaemia

• Hypocalcaemia
  – The serum calcium is below the reference range
  – Watch out for false results
    • Low serum albumin

• Hypercalcaemia
  – The serum calcium is above the reference range
  – Watch out for false results
    • Leave on the tourniquet for too long
Causes of Hypercalcaemia

• **Primary hyperparathyroidism**
  – Usually a single adenoma
  – May be familial, when it is hyperplasia of several glands
  – Common condition in postmenopausal women
  – Commonest cause in outpatients or GP setting

• **Hypercalcaemia of malignancy**
  – The diagnosis of cancer is usually obvious
  – Commonest cause in inpatient setting

• **Lots of other causes, but less common**
Note – the calcium excretion (or urinary calcium) may be low for a given level of serum calcium, but it is still often increased above normal and so the risk of kidney stones is increased.
Tumours produce a variety of factors that can stimulate bone resorption, such as parathyroid hormone related protein (PTHrP).

PTHrP has a similar structure to PTH and works in the same way as PTH (it binds to the PTH receptor) but it is not measured by the PTH assay.
Consequences of Primary Hyperparathyroidism

‘Bones, stones, groans and abdominal moans..’

- **Bone disease**
  - Osteitis fibrosa cystica
  - Osteoporosis

- **Kidney**
  - Stones
  - Nephrogenic diabetes insipidus
    - Is common in a mild form causing thirst and polyuria

- **Fatigue; confusional state due to dehydration**

- **Abdominal pain**
  - Constipation (due to dehydration)
  - Acute pancreatitis

Note – these are all consequences of hypercalcaemia, except for the bone disease which is specific to primary hyperparathyroidism
Primary Hyperparathyroidism

The arrows show sub-periosteal erosions of the phalanges

The skull shows cysts ‘Osteitis fibrosa cystica’
Relationship between Serum Calcium and Parathyroid Hormone in Disorders of Calcium Homeostasis

- **Parathyroid disease**
  - Low serum calcium
    - Hypoparathyroidism
    - Low PTH
  - High serum calcium
    - Primary hyperparathyroidism
    - High PTH

- **Non-parathyroid disease**
  - Low serum calcium
    - Osteomalacia
    - High PTH
    - Secondary hyperparathyroidism
  - High serum calcium
    - Hypercalcaemia of malignancy
    - Low PTH
Disorders of Calcium Homeostasis
Disorders of Calcium Homeostasis

- Osteomalacia
- Primary Hyperparathyroidism
- Hypoparathyroidism
- Hypercalcaemia of Malignancy

Graph showing PTH (ng/mL) on the Y-axis and Calcium (mmol/L) on the X-axis.
Disorders of Phosphate Homeostasis
Disorders of Phosphate Homeostasis

Outline

• Brief revision of phosphate physiology
• Definitions
  – Hypophosphataemia and hyperphosphataemia
• Causes and consequences
  – Osteomalacia and rickets
  – Tumoral Calcinosis
• Illustrative cases
Summary of Phosphate Homeostasis Response to an Increase in Serum Phosphate

- sPi
- FGF-23
- PTH
- Bone Resorption
- Pi Reabsorption
- 1,25-(OH)₂ vit D
- Pi Absorption
- u-phos
Clinical Features of Hypophosphataemia

• Rickets and osteomalacia
  – Without any symptoms of hypocalcaemia
• The likely cause of the impaired mineralisation is the low serum calcium-phosphate product
• The biochemical changes
  – Low serum phosphate
  – High alkaline phosphatase
  – Normal serum calcium and PTH
Causes of Hypophosphataemia

• Too little phosphate intake
  – Diet
  – Phosphate binders (aluminium hydroxide)

• Shift of phosphate into cells
  – Intravenous glucose and insulin

• Renal phosphate leak
  – Tumor-induced
  – X-linked
  – Others
Control of Phosphate Metabolism

FGF-23 fragments, inactive

PHEX

FGF-23

Decreased expression of Na-P co-transporters
Inhibition of Tubular Phosphate Reabsorption
Phosphaturia

Downregulation of renal 1-alpha hydroxylase
Low to normal 1,25-D

Hypophosphataemia

Jan de Beur, SM. JAMA. 2005 Sep 14;294(10):1260-7
Pathogenesis of Tumour-Induced Osteomalacia

FGF-23 fragments, inactive

Abnormality
- Increased FGF-23 by tumour

PHEX

Decreased expression of Na-P co-transporters
Inhibition of Tubular Phosphate Reabsorption
Phosphaturia

FGF-23

Downregulation of renal 1-alpha hydroxylase
Low to normal 1,25-D

Hypophosphataemia

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Pathogenesis of X-Linked Hypophosphataemic Rickets

- **Abnormality**
  - Mutation in PHEX gene

- **FGF-23 fragments, inactive**

**PHEX**

- Decreased expression of Na-P co-transporters
- Inhibition of Tubular Phosphate Reabsorption
- Phosphaturia

**FGF-23**

- Downregulation of renal 1-alpha hydroxylase
- Low to normal 1,25-D

**Hypophosphataemia**
Clinical Features of Hyperphosphataemia

- **Tumoral calcinosis**
  - Calcific deposits around shoulder and pelvis
    - The calcium-phosphate product is high
  - High levels of
    - Serum phosphate
    - 1,25-D
Calcific Deposits around Right Hip
Causes of High Serum Phosphate

- Chronic renal failure – decreased phosphate excretion
- Hypoparathyroidism – decreased PTH levels
- Tumoral Calcinosis – low FGF-23
- Increased catabolism, e.g. diabetic ketoacidosis
Pathogenesis of Tumoral Calcinosis

Abnormalities
- Decreased production of FGF-23
- Abnormal glycosylation and accelerated degradation – GALNT3

FGF-23 fragments, inactive

PHEX

Increased expression of Na-P co-transporters
Increase in Tubular Phosphate Reabsorption
Low urine phosphate excretion

Upregulation of renal 1-alpha hydroxylase
High to normal 1,25-D

Hyperphosphataemia

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Disorders of Magnesium Homeostasis
Clinical Features of Hypomagnesaemia

• Fatigue and muscle weakness
• Hypocalcaemia and hypokalaemia
  – Tetany, epilepsy
Causes of Hypomagnesaemia

- Too little magnesium intake
  - Diet
- Loss of magnesium into intestine
  - Fistulas
- Renal magnesium leak
  - Alcohol-induced; PPI (omeprazole)
  - Genetic
  - Others