Bone Metabolism and Calciotropic Hormones

Richard Eastell
Professor of Bone Metabolism
Academic Unit of Bone Metabolism
University of Sheffield
Past President of ECTS
Distribution of Calcium in the Body

• Skeleton is main reservoir
  – 1200 g

• Extracellular space has much smaller amount of calcium (only 1 g), but it is key for cell function
  – Normal blood clotting
  – Muscle contractility
  – Nerve function
Calcium Kinetics

- Ca$^{2+}$ absorption
- Bone resorption
- Extracellular Fluid Ca$^{2+}$
- Bone formation
- Endogenous Fecal Ca$^{2+}$
- Ca$^{2+}$ excretion
- Ca$^{2+}$ reabsorption
Dietary Calcium

- **Major sources**
  - Dairy products make up 2/3
    - Milk, yoghurt, cheese
- **Minor sources**
  - Vegetables, e.g. broccoli
  - Cereals, e.g. white bread
  - Oily fish, e.g. sardines
Calcium absorption

- We absorb about 30% of dietary calcium
  - Active absorption in duodenum and jejunum
  - Passive absorption in ileum and colon
- We absorb a higher fraction of calcium when put on a low calcium diet
  - This is mediated by 1,25-(OH)_2 vitamin D, the active form of vitamin D
  - Most calcium is absorbed by active transport
Release of Calcium from Bone

• Calcium can be released rapidly from exchangeable calcium on the bone surface
  – We don’t know much about this mechanism
• Calcium can be released more slowly by osteoclasts during bone resorption
Calcium Handling by the Kidney

- The amount of calcium filtered by the glomerulus depends on
  - The glomerular filtration rate
  - The ultrafiltrable calcium
    - Ionised
    - Complexed

- 98% of this filtered calcium is usually reabsorbed
  - More is reabsorbed if the PTH level is high
  - Less is reabsorbed if the filtered sodium is high
Calcium and Phosphate Excretion
Reabsorption by the Nephron

**CALCIUM**

- **Glomerulus**
  - Passive: 65%
  - Active: 8%

- **Distal Renal Tubule**
  - Passive: 25%
  - Active: 80%

**PHOSPHATE**

- **Glomerulus**
  - Passive: 10%
  - Active: 80%

- **Distal Renal Tubule**
  - Passive: 25%
  - Active: 10%

**Fractional Excretion**
- Fractional Excretion of Calcium = 2%
- Fractional Excretion of Phosphate = 10%
The Regulation of Serum Calcium
Secretion of Parathyroid Hormone

Serum Calcium \arrow{up}

Parathyroid Hormone

4 parathyroid glands
Calcium acts on the calcium sensing receptor

Intact PTH, 1 to 84

Degradation occurs within minutes of secretion

PTH Fragments
Note how small changes in serum calcium result in big changes in PTH.
Relationship Between Serum Calcium and PTH - 2

RELATIONSHIP BETWEEN PTH AND CALCIUM

- PTH secretion rate (units/body weight/min)
- Plasma calcium (mmol/l)

www.shef.ac.uk/aubm
VITAMIN D
Biosynthesis

Skin

Intestine

Liver

Kidney

7-Dehydrocholesterol

UV - B

Vitamin D

25 - hydroxylase

25-OH vitamin D

24 - hydroxylase

1α - hydroxylase

1,25-(OH)₂ vitamin D

24,25 (OH)₂vit D

1,24,25 (OH)₃vit D

Calcitroic Acid

1,25-(OH)₂ vitamin D

↑PTH

↓phos

↓Ca²⁺
Seasonal and geographical variation in the prevalence of hypovitaminosis D (25-hydroxyvitamin D <40 nmol/L) in Great Britain

Calcitonin

- Hormone produced by C cells in the thyroid
- Its secretion is stimulated by an increase in serum calcium
- Its effect is to lower bone resorption
- The importance in man is uncertain
  - It is much more important in animals living in a high calcium environment, e.g. fish
Parathyroid Hormone Actions

- Ca$^{2+}$ reabsorption
- Phosphate Reabsorption
- $1\alpha$-hydroxylation of 25-OH vitamin D
- Bone Remodelling
- Bone Resorption > Bone Formation
- No direct effect
- Ca$^{2+}$ absorption because of increased 1,25-(OH)$_2$ vitamin D
Calcium and Phosphate Excretion Regulation by PTH

**CALCIUM**

- Passive: 65%
- Passive: 25%
- Active: 8%

**PHOSPHATE**

- Passive: 80%
- Passive: 10%
- Active: 25%

**Distal Renal Tubule**

- PTH increases calcium reabsorption by the distal renal tubule

- Fractional Excretion of Calcium = 1%
- Fractional Excretion of Phosphate = 20%

**Glomerulus**

- PTH decreases phosphate reabsorption by the proximal renal tubule
Summary of Calcium Homeostasis
Response to a Decrease in Serum Calcium

- sCa\(^{2+}\)
- PTH
- u-phos
- s-phos
- 1,25-(OH)\(_2\) vitamin D
- Ca\(^{2+}\) reabsorption
- Ca\(^{2+}\) absorption

Bone Resorption
Example of Adaptation
Response to a Low Diet Calcium

• Low dietary calcium means,
• Less calcium is absorbed,
• This results in lower serum ionised calcium,
• This results in higher PTH,
• This results in fast and slow actions
  – Fast action, increased flux of calcium from bone and decreased excretion of calcium from kidney
  – Slow action, increased bone resorption, and increased fractional absorption by the intestine
• This returns serum ionised calcium to normal
Disorders of Calcium Homeostasis
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 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

**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
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**
Primary Hyperparathyroidism

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.
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’.
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.
Phosphate Homeostasis
Summary of Phosphate Homeostasis
Response to an Increase in Serum Phosphate

sPi  \rightarrow \downarrow \text{Pi reabsorption}
\uparrow \text{FGF-23*}
\rightarrow \uparrow \text{Bone Resorption}
\rightarrow \downarrow \text{Pi absorption}
\rightarrow \downarrow \text{1,25-(OH)}_2\text{ vitamin D}
\rightarrow \downarrow \text{u-phos}

\text{PTH}

* FGF-23, fibroblast growth factor 23
Disorders of Phosphate Homeostasis
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
Pathogenesis of Tumour-Induced Osteomalacia

Abnormality
- Increased FGF-23 by tumour

FGF-23

FGF-23 fragments, inactive

PHEX

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
Pathogenesis of X-Linked Hypophosphataemic Rickets

Abnormality

• Mutation in PHEX gene

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
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 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

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

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

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

Hyperphosphataemia
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
Bone Metabolism and Calciotropic Hormones

Thanks for your attention