

Lecture: 9

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Fifth Stage

Clinical Chemistry

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Disorders of Calcium Metabolism

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The total body calcium depends upon the calcium absorbed from dietary intake and that lost from the body. **Ninety-eight per cent** of body calcium is found in the skeleton. The **extra osseous fraction** 'although amounting to **only one per cent** of the total 'is essential because of its effect on **neuromuscular excitability** and **cardiac muscle**. An important mediator of intracellular calcium is **calmodulin**, a calcium-binding regulatory protein.

Factors affecting calcium intake

1. The amount of calcium in diet.
2. The active metabolite of vitamin D, 1,25-dihydroxycholecalciferol (1,25-(OH)₂ D₃, also called **calcitriol**), is **needed for calcium absorption**.
3. Calcium in the intestine may form insoluble, poorly absorbed complexes with oxalate, phosphate.
4. An excess of fatty acids in the intestinal lumen in steatorrhoea may contribute to calcium malabsorption.

Factors affecting calcium loss

1. Urinary calcium excretion depends on:
 - a. The amount of calcium reaching the glomeruli.
 - b. The glomerular filtration rate (GFR).
 - c. Renal tubular function.
2. Parathyroid hormone and **1,25-dihydroxyvitamin D** **increase urinary calcium reabsorption**.

Plasma calcium

The plasma calcium is present in **two** main forms:

- A. Calcium bound to proteins**, mainly albumin: this accounts for a little less than **half** the total calcium concentration and is the physiologically **inactive** form.

B. Free ionized calcium, which comprises most of the rest. This is the physiologically **active** fraction.

Changes in plasma protein concentration, particularly of albumin, alter the most commonly measured concentration, that of **plasma total calcium**, but not that of the **free ionized fraction**. The **plasma total** (but not free ionized) calcium concentration is **lower** in the **supine** than in the **erect** position **because of the effect of posture on fluid distribution** and therefore on plasma protein concentration. The direct measurement of the physiologically active free calcium ionized fraction is, for technical reasons. **Formulae** incorporating the albumin concentration have been devised in an attempt to calculate the active fraction of the plasma total calcium concentration. The following is a commonly used formula:

$$\text{plasma albumin-adjusted} \quad \text{or} \quad \text{'corrected' calcium (mmol/L)} = \\ \text{plasma measured calcium} + (40 - \text{plasma[albumin]} \text{ (g/L)} \times 0.02)$$

Changes in plasma hydrogen ion concentration ($[H^+]$) affect the binding of calcium to plasma proteins because H^+ competes with Ca^{2+} for binding sites. The **plasma total calcium concentration is unaltered** by changes in $[H^+]$.

If $[H^+]$ falls, as in an **alkalosis**, increases binding and so decreases the proportion of plasma calcium in the **free ionized**, despite a **normal plasma total calcium concentration**, form **tetany** may occur. Conversely, an **acidosis** (increase $[H^+]$) decreases binding and so increases the proportion of plasma calcium in the **free ionized form**. Also, by **increasing calcium solubility**, it **increases the rate of release of calcium from bones** into the extracellular fluid (ECF). The increased load reaching the kidneys increases the renal calcium loss. **Prolonged acidosis** may cause **osteomalacia**.

Control of plasma calcium

There are a number of mechanisms by which plasma calcium concentrations are controlled. The effectiveness of this control depends upon:

1. An adequate supply of: A. Calcium B. Vitamin D

2. Normal functioning of the: A. Intestine B. Parathyroid glands C. Kidneys

1. Parathyroid hormone

Parathyroid hormone (PTH) is a single chain polypeptide containing 84 residues. The biological actions of PTH include:

A- Stimulation of osteoclastic bone resorption, so releasing both **free ionized calcium** and phosphate into the ECF; this action **increases** the plasma concentrations of both **calcium** and **phosphate**.

B- Decreased renal tubular reabsorption of phosphate, causing phosphaturia and increased reabsorption of calcium; this action tends to **increase** the plasma **calcium** concentration but to **decrease** the **phosphate**.

The **control of PTH secretion depends on the concentration of free ionized calcium** in blood circulating through the parathyroid glands. A **fall of free ionized calcium increases the rate of PTH secretion**, which, under physiological conditions, continues until the calcium concentration returns to normal.

2. Parathyroid hormone-related protein

Parathyroid hormone-related protein (PTHRP) is a peptide hormone that has a similar amino acid sequence at the biologically active end of the peptide, therefore **activating the same receptors as PTH**. The function of PTHRP is uncertain, but it may be important in calcium metabolism in the fetus. The **gene that codes for PTHRP** is widely distributed in body tissues but is **normally repressed**. However, it may be **activated in certain tumours**, causing **humoral hypercalcaemia of malignancy**.

3. Calcitonin

Calcitonin (produced in the **C cells of the thyroid gland**) decreases osteoclastic activity, **slows calcium release from bone** and has the **opposite effect** on plasma concentrations of **PTH**.

4. Vitamin D

Vitamin D is derived from **ergocalciferol** (vitamin D₂), obtained from **plants** in the diet and **cholecalciferol** (vitamin D₃), formed in the **skin** by the action of ultraviolet light on 7-dehydrocholesterol, this is the form found in **animal tissues**, especially the liver. Vitamin D is transported in plasma bound to specific carrier proteins. **It is inactive until metabolized**. In the **liver**, cholecalciferol is hydroxylated to 25-hydroxycholecalciferol (**25-OHD₃**) by the enzyme **25-hydroxylase**. In the proximal renal tubular cells of the **kidney**, 25-OHD₃ undergoes a second hydroxylation, catalysed by the enzyme **1- α -hydroxylase** to form the **active metabolite** **1,25-(OH)₂D₃** called **calcitriol**.

The activity of **1- α -hydroxylase**, and hence the production of **1,25-(OH)₂D₃**, may be **stimulated by**:

1. A low plasma phosphate concentration
2. An increase in plasma PTH concentration.

The activity of **1- α -hydroxylase**, and hence the production of **1,25-(OH)₂D₃**, may be **inhibited by**:

1. Hyperphosphataemia
2. High levels of free ionized calcium

The kidney is an endocrine organ, synthesizing and releasing the hormone **1,25-(OH)₂D₃** (**calcitriol**); impairment of the final hydroxylation helps explain the **hypocalcaemia of renal disease**. The biological **actions** of this hormone include:

- 1- Increases calcium absorption by intestinal mucosal cells.
- 2- In conjunction with PTH, it increases osteoclastic activity, releasing calcium from bone.

5. Calcium-sensing receptor

The **calcium-sensing receptor (CaSR)** is a G protein-coupled receptor. This **allows** the **parathyroid cells** and the **ascending loop of Henle epithelial cells** to **respond to changes in extracellular calcium**. The parathyroid cell surface is rich in CaSR, which **allows PTH secretion to be adjusted rapidly depending** on the **calcium concentration**.

Defects in the CaSR gene are responsible for various rare defects of calcium

homeostasis. Inactivating mutations include familial benign **hypocalciuric hypercalcaemia**.

6. Miscellaneous mechanisms of calcium control

Thyroid hormone excess may be associated with **increased fecal and urinary excretion** of **calcium**, probably following its **release from bone**. Other hormones influencing calcium metabolism include **oestrogens, prolactin and growth hormone**. These may increase $1,25\text{-}(\text{OH})_2\text{D}_3$ production and **increase calcium absorption**.

Disorders of calcium metabolism

1. Hypercalcaemia

Clinical effects of hypercalcaemia

1. Renal effects:

- a. Renal damage**, because of the **high plasma free ionized calcium** concentration, the solubility of **calcium phosphate** may be exceeded and **precipitate** in the kidneys.
- b. Polyuria**, may result from impairment of renal concentrating ability owing to calcification of the tubular cells; acute hypercalcaemia may cause reversible **inhibition** of the tubular response **to antidiuretic hormone** rather than to cell damage.
- c. Renal calculi**, may be caused by **precipitation of calcium salts** in the urine.
- d. Hypokalaemia**, calcium may directly **inhibit potassium reabsorption** from the tubular lumen.

2. Depress neuromuscular excitability in both voluntary and involuntary muscle.

There may also be muscular hypotonia.

3. Depression, anorexia, nausea and vomiting, associated with high plasma calcium concentrations, are probably caused by an effect on the central nervous system.

4. Peptic ulceration, calcium stimulates gastrin (and therefore gastric acid) secretion.

The patient may complain of constipation and abdominal pain.

5. Severe hypercalcaemia causes characteristic changes in the **electrocardiogram** (ECG). If plasma concentrations exceed about 3.5 mmol/L, there is a risk of sudden cardiac arrest or ventricular arrhythmias.

Causes of hypercalcaemia

1. Primary hyperparathyroidism

This is caused by inappropriate secretion of PTH by the parathyroid glands, causing hypercalcaemia. It is usually due to **parathyroid adenomas** or **carcinoma** of the glands. The majority of cases of primary hyperthyroidism is characterized by **high plasma PTH** and **high plasma calcium** with **low plasma phosphate** concentrations.

2. Tertiary hyperparathyroidism

This may occur if the parathyroid glands have been subjected to long standing hypocalcaemia of secondary hyperparathyroidism which have been subsequently corrected. The **parathyroid glands hypertrophy**; PTH secretion becomes partly **autonomous** and is not suppressed by negative feedback by the hypercalcaemia. The **diagnosis is usually made when the cause of the original hypocalcaemia is removed**, for example by renal transplantation or correction of long standing calcium or vitamin D deficiency as in malabsorption. **A history of previous hypocalcaemia** and **the finding of a very high plasma alkaline phosphatase** activity due to the prolonged osteomalacia **distinguish it from primary hyperparathyroidism**.

3. Hypercalcaemia of malignancy

a. Malignant disease of bone: Some patients with multiple bony metastases (for example from breast, lung, prostate and kidney tumours) or with multiple myeloma show hypercalcaemia. The **hypercalcaemia** is caused by **direct bone breakdown**. Here there is usually a **parallel rise of plasma phosphate** and a **rise in plasma alkaline phosphatase activity**.

b. Humoral hypercalcaemia of malignancy:

Parathyroid hormone-related protein is synthesized by some malignant tumours of non endocrine tissues and is **not subject to normal feedback control** by the high plasma free ionized calcium concentration. In humoral hypercalcaemia of malignancy, the plasma **calcium** concentration may **rise from normal to dangerously high very rapidly**, in contrast to primary hyperparathyroidism.

4. Drugs/medications

Various medications can evoke hypercalcaemia, such as **thiazides** (decreases calcium renal excretion) and **lithium**.

5. Milk–alkali syndrome

This condition occurs with the excessive use of **calcium containing antacids** for dyspepsia.

6. Vitamin D excess

Vitamin D excess may be caused by **over vigorous treatment** of hypocalcaemia. Increased intestinal calcium absorption may cause dangerous hypercalcaemia.

7. Sarcoidosis

1,25-Dihydroxycholecalciferol is **synthesized in the granuloma tissue** and increases calcium absorption from the intestinal tract. Chronic beryllium poisoning produces a granulomatous reaction very similar to that of sarcoidosis and may also be associated with hypercalcaemia.

8. Hypercalcaemia of hyperthyroidism

Prolonged excess of thyroid hormone in **severe hyperthyroidism** may be associated with hypercalcaemia. Hypercalcaemia is a very rare complication.

9. Other endocrine causes of hypercalcaemia

These include acromegaly, Addison's disease and phaeochromocytoma.

10. Familial hypocalciuric hypercalcaemia

Hypercalcaemia with an **inappropriately high plasma PTH** concentration in the presence of **hypocalciuria** has been reported in some families. The **aetiology** of the

condition is thought to be due a defect on the CaSR (found in parathyroid gland and kidney). This defect lead to stimulation of PTH secretion and decrease the urinary calcium excretion from the kidney.

2. Hypocalcaemia

Clinical effects of hypocalcaemia

Low calcium concentrations cause increased neuromuscular activity eventually leading to tetany, generalized seizures, paraesthesiae and hypotension. Hypocalcaemia may also cause depression and cardiac arrhythmias, including prolonged Q-T interval on ECG.

A. Hypocalcaemia with hypophosphataemia

Hypocalcaemia with hypophosphataemia resulted from reduction in calcium and vitamin D that resulted from:

1. In steatorrhoea, fat and therefore vitamin D absorption is impaired, calcium combines with unabsorbed fatty acids to form insoluble soaps in the lumen.
2. Deficiency due to under nutrition is more commonly caused by deficiency of vitamin D than of calcium.
3. Impaired metabolism of vitamin D to $1,25\text{ (OH)}_2\text{D}_3$ due to renal disease.
4. Chronic liver disease may occasionally be associated with mild osteomalacia. This is resulted from impairment of vitamin D hydroxylation in the liver.
5. Prolonged anticonvulsant therapy, especially if both barbiturates and phenytoin are taken, may be associated with hypocalcaemia and even osteomalacia. These drugs probably induce the synthesis of hepatic enzymes which catalyse the conversion of vitamin D to inactive metabolites.

In all these conditions, secondary hyperparathyroidism ('appropriate' secretion of PTH) occurs in response to a low plasma free ionized calcium concentration. High plasma PTH concentrations cause phosphaturia with hypophosphataemia if glomerular function is normal. (i.e. secondary hyperparathyroidism is characterized

by high plasma PTH and low plasma calcium with low plasma phosphate concentration).

Without an adequate supply of calcium and phosphate, osteoid cannot be calcified despite marked osteoblastic proliferation. The histological finding of **uncalcified osteoid** is characteristic of **osteomalacia in adults** or **rickets in children**. Plasma alkaline phosphatase activity is increased because of osteoblastic proliferation.

B. Hypocalcaemia with hyperphosphataemia

1. Renal dysfunction

Renal disease such as chronic kidney disease causes **relative resistance to vitamin D** because of the effect of the **disease** on the functioning renal tubular cells and therefore on 1- α -hydroxylation of 25-OHD₃ and inhibition of 1- α -hydroxylation by **hyperphosphataemia** associated with the low GFR of renal glomerular dysfunction.

2. Primary hypoparathyroidism

Hypoparathyroidism is usually caused by **surgical damage to the parathyroid glands**, either directly or indirectly by impairment of their blood supply during partial thyroidectomy. **Total thyroidectomy** or **laryngectomy** is often associated with removal or damage to the parathyroid glands and it is important to monitor plasma calcium concentrations. **Primary hypoparathyroidism** is characterized by **low plasma PTH** and **low plasma calcium** with **high plasma phosphate** concentration.

3. Pseudohypoparathyroidism

This is a **very rare inborn error** associated with an **impaired response of both kidneys and bone to PTH**, that is, **end organ resistance to circulating PTH**. Thus plasma **PTH** concentration is **raised** with **hypocalcaemia**.