Calcium disorders

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- Disorders of calcium metabolism are common in clinical practice and may result in hypocalcaemia or hypercalcaemia as well as bone abnormalities. Intimately associated with calcium disorders are disorders involving phosphate and magnesium metabolism.

Calcium metabolism

- **TOTAL BODY CALCIUM**
- The total body calcium depends upon the calcium absorbed from dietary intake and that lost from the body (Fig. 6.1). Ninety-eight per cent of body calcium is found in the skeleton.

- The extraosseous fraction, although amounting to only 1 per cent of the total,is essential because of its effect on neuromuscularexcitability and cardiac muscle An important mediator of intracellular calcium is calmodulin, a calciumbinding
- regulatory protein.

Factors affecting calcium intake

- About 25 mmol (1 g) of calcium is ingested per day, of which there is a net absorption of 6–12 mmol (0.25–0.5 g). The active metabolite of vitamin D, 1,25-dihydroxycholecalciferol (1,25-(OH)2D3, also called calcitriol), is needed for calcium absorption.

- Factors affecting calcium loss
- Calcium is lost in urine and faeces. Urinary calcium excretion depends on the amount of calcium reaching the glomeruli, the glomerular filtration rate (GFR) and renal tubular function. Parathyroid hormone and 1,25-dihydroxyvitamin D increase urinary calcium reabsorption.

- Faecal calcium is derived from the diet and that portion of the large amount of intestinal secretions that has not been reabsorbed. Calcium in the intestine

CONCEPT OF PLASMA CALCIUM AND ALBUMIN CORRECTION (ADJUSTED)

- The mean plasma calcium concentration in healthy subjects is tightly controlled, at around 2.15–2.55 mmol/L, and is present in two main forms:
- *Calcium bound to proteins*, mainly albumin: this accounts for a little less than half the total calcium concentration as measured by routine analytical methods and is the physiologically inactive form. *Free ionized calcium* (Ca2+), which comprises most of the rest. This is the physiologically active fraction.

- Changes in plasma hydrogen ion concentration ([H+]) affect the binding of calcium to plasma proteins because H+ competes with Ca2+ for binding sites. The plasma total calcium concentration is unaltered by changes in [H+]. If [H+] falls, as in an alkalosis, tetany may occur, despite a normal plasma total calcium concentration.

- Conversely, an acidosis 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, partly due to the buffering effect of bone.

Control of plasma calcium

- There are a number of mechanisms by which plasma calcium concentrations are controlled. Calcium homeostasis follows the general rule that extracellular concentrations are controlled rather than the total body content.

- The effectiveness of this control depends
- upon:
- an adequate supply of:
- – calcium,
- – vitamin D,
- normal functioning of the:
- – intestine,
- – parathyroid glands,
- – kidneys.
- If any one of these factors is impaired, calcium leaves
- bone by passive physicochemical diffusion, and plasma
- concentrations may be maintained at the expense of
- bone calcifi cation.

Parathyroid hormone

- Parathyroid hormone (PTH) is a single-chain polypeptide containing 84 residues, with its 34 N-terminal amino acids largely determining its biological activity. It is metabolized by renal, hepatic and bone cells.

- The biological actions of PTH include:
- 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,

- 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 increases the rate of PTH secretion, which, under physiological conditions, continues until the calcium concentration returns to normal. The secretion of PTH is also affected by the extracellular magnesium concentration, being decreased by severe, chronic hypomagnesaemia.

- 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

- 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. It is probably less important than PTH in physiological homeostasis

- Plasma concentrations may be very high in patients with medullary carcinoma of the thyroid, although hypocalcaemia is not usually reported in this condition. However, exogenous calcitonin has been used to treat hypercalcaemia and Paget's disease of bone.

Metabolism and action of vitamin D

- Vitamin D is derived from:
- ergocalciferol (vitamin D2), obtained from plants in the diet,
- cholecalciferol (vitamin D3), formed in the skin by the action of ultraviolet light on 7-dehydrocholesterol (Fig. 6.2); this is the form found in animal tissues, especially the liver.

- In normal adults, much more cholecalciferol is derived from the action of sunlight on skin (wavelength 270–310 nm) than from food. Dietary sources are important when requirements are high, such as during growth or pregnancy, or in those elderly or chronically sick individuals who are confi ned indoors and not exposed to the sun.

- 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. The rate of formation of 25-OHD3 is affected by the supply of substrate in the form of calciferol, whether derived from the skin or from the

- diet. It is the main circulating form and store of the vitamin. Other hydroxylated metabolites are found, such as 24,25-(OH)2D3. In the proximal renal tubular cells of the kidney, 25-OHD3 undergoes a second hydroxylation, catalysed by the enzyme 1-a-hydroxylase to form the active metabolite 1,25-(OH)2D3.

- The activity of 1-a-hydroxylase, and hence the
- production of 1,25-(OH)2D3, may be stimulated by:
- a low plasma phosphate concentration, an increase in plasma PTH concentration, possibly because of its phosphate-lowering effect. Its activity is inhibited by:
- hyperphosphataemia,
- high levels of free ionized calcium.

- The kidney is an endocrine organ, synthesizing and releasing the hormone 1,25-(OH)2D3; impairment of the final hydroxylation helps explain the hypocalcaemia of renal disease. This hormone increases calcium absorption by intestinal mucosal cells. In conjunction with PTH, it stimulates osteoclastic activity, releasing calcium from bone.

- The action of PTH on bone is impaired in the absence of 1,25-(OH)2D3. A fall in plasma free ionized calcium concentration stimulates PTH secretion. The PTH enhances 1-a-hydroxylase activity and therefore stimulates 1,25-(OH)2D3 synthesis.

- The two hormones act synergistically on the osteoclasts of bone, releasing calcium into the circulation; 1,25-(OH)2D3 also increases calcium absorption from the intestinal lumen. In the short term, the homeostatic mechanisms involving the effects on bone are the more important; if

- hypocalcaemia is prolonged, more effi cient absorption becomes important. Once the plasma free ionized calcium concentration is adjusted, the secretion of both PTH and 1,25-(OH)2D3 is suppressed

- Thus, 25-OHD3 is the circulating, inactive form of vitamin D and plasma concentrations fall in deficiency states. The measurement of the biologically active metabolite, 1,25-(OH)2D3, which circulates in plasma bound to vitamin D-binding protein (VDBP) in very low concentrations, is rarely indicated unless a defect in the vitamin metabolic pathway is suspected, as it does not reflect body stores.

- Calcium-sensing receptor
- The calcium-sensing receptor (CaSR) is a G proteincoupled 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 and neonatal severe hyperparathyroidism; activating mutations include autosomal dominant hypocalcaemia with hypercalciuria. Calcimimetic agents have been devised that bind and activate the CaSR, resulting in decreased PTH release and reduced plasma calcium concentrations.

- **DISORDERS OF CALCIUM METABOLISM**
- The consequences of most disturbances of calcium metabolism can be predicted from knowledge of the actions of PTH on bone and on renal tubular cells, and from plasma concentrations of calcium and phosphate.

- A low plasma free ionized calcium concentration normally stimulates PTH secretion, which results in phosphaturia; the loss of urinary phosphate over-rides the tendency to hyperphosphataemia due to the action of PTH on bone.

- Consequently, the plasma phosphate concentration is usually low when the plasma PTH concentration is increased. Conversely, a high plasma free ionized calcium concentration, unless due to inappropriate excess of PTH, inhibits PTH secretion and causes a high plasma phosphate concentration.

- Therefore plasma calcium and phosphate concentrations usually vary in the same direction unless: renal glomerular dysfunction is severe enough to impair the phosphaturic (and therefore hypophosphataemic) effect of PTH or PTHRP, there is inappropriate excess or deficiency of PTH due to a primary disorder of the parathyroid gland or to secretion of PTHRP; in such cases calcium and phosphate vary in opposite directions.

- Hypercalcaemia
- Clinical effects of an increased plasma albuminadjusted
- calcium concentration
- Renal effects.
- – *Renal damage* is one of the most serious clinical
- consequences of prolonged hypercalcaemia.
- Because of the high plasma free ionized calcium
- concentration, the solubility of calcium
- phosphate may be exceeded and precipitate
- in extraosseous sites such as the kidneys

- *Polyuria*, characteristic of chronic hypercalcaemia, may result from impairment of renal concentrating ability owing to calcifi cation of the tubular cells; acute hypercalcaemia may cause reversible inhibition of the tubular response to antidiuretic hormone rather than to cell damage. These effects can lead to dehydration.

- *Renal calculi*, without signifi cant parenchymal damage, may be caused by precipitation of calcium salts in the urine if the free ionized calcium concentration is high in the glomerular filtrate owing to hypercalcaemia

- *Hypokalaemia*, often with a metabolic alkalosis, is associated with hypercalcaemia. Calcium may directly inhibit potassium reabsorption from the tubular lumen

- High extracellular free ionized calcium concentrations can depress neuromuscular excitability in both voluntary and involuntary muscle. There may also be muscular hypotonia.
- Depression, anorexia, nausea and vomiting, associated with high plasma calcium concentrations, are probably caused by an effect on the central nervous system

- Calcium stimulates gastrin (and therefore gastric acid) secretion. There is an association between chronic hypercalcaemia and peptic ulceration. The patient may complain of constipation and abdominal pain. Hypercalcaemia may also present as an acute abdomen.

- Some patients with hypercalcaemia may be hypertensive. If renal damage is not severe, the hypertension may respond to reducing the plasma calcium concentration. Severe hypercalcaemia causes characteristic changes in the electrocardiogram (ECG), with shortening of

- the Q–T interval and broadening of the T waves. If plasma concentrations exceed about 3.5 mmol/L, there is a risk of sudden cardiac arrest or ventricular arrhythmias. For this reason severe hypercalcaemia should be treated as a matter of urgency.
- Hypercalcaemia is also associated with bone and joint pain.

- Hypocalcaemia
- Clinical effects of a reduced albumin-adjusted plasma calcium concentration Low plasma albumin-adjusted calcium concentrations, including those associated with a normal total calcium concentration of alkalosis, cause increased neuromuscular activity eventually leading to tetany and carpopedal spasm, generalized seizures, laryngospasm,
- hyper-reflexia, paraesthesiae and hypotension

- Prolonged hypocalcaemia, even when mild, interferes with the metabolism of the lens in the eye and may cause cataracts. Because of this, asymptomatic hypocalcaemia should be sought when there has been a known risk of parathyroid damage, such as after partial or total thyroidectomy, and, if found, treated.

- Latent neuromuscular hyperactivity, carpopedal
- spasm and tetany (Trousseau’s sign) can be evoked by
- infl ating a blood pressure cuff to 10–20 mmHg above
- systolic blood pressure for 3–5 min. Chvostek’s sign
- can be elicited by tapping the facial nerve anterior to
- the ear, when ipsilateral facial muscle contraction may
- occur, although this can also occur in about 10 per cent
- of individuals without hypocalcaemia.

- It is sometimes useful to divide hypocalcaemia into those cases with a low plasma phosphate concentration (hypophosphataemia) and those with high plasma phosphat concentration (hyperphosphataemia), although not all cases of hypocalcaemia fall neatly into this classification

- Thank you