Advanced Clinical Biochemistry

Hormonal regulation calcium, phosphate, and magnesium metabolism

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Calcium homeostasis

The amount of calcium present in extracellular fluid is very small in comparison to that stored in bone. Even in the adult, calcium in bone is not static; some bone is resorb calcium each day and the calcium returned to the ECF. To maintain calcium balance, an equal amount of bone formation must be take place.
Calcium homeostasis is modulated by hormones

- **Parathyroid hormone** (PTH), which consists of 84 amino acids, is secreted from the parathyroid glands in response to a low unbound plasma calcium.

**PTH** causes bone resorption and promotes calcium reabsorption in the renal tubules, preventing loss in the urine.
1,25-dihydroxycholecalciferol (1,25DHCC) maintains intestinal calcium absorption. The sterol hormone is formed from vitamin D (cholecalciferol) following hydroxylation in the liver (at carbon 25) and kidney (at carbon 1).
- Calcitonin secreted from C cells of thyroid gland, stimulates the uptake of Ca++ into bones, thus lowering its level in the blood, opposite PTH action.
Serum calcium

A healthy person has a total serum calcium of around 2.4 mmol/L. About half is bound to protein, mostly to albumin. Binding is pH dependent and is decreased in acidosis, while binding is increased if an alkalosis is present.
Unbound calcium is the biologically active fraction of the total calcium in plasma and maintenance of its concentration within tight limits is required for:

- **Nerve function**
- **Membrane permeability**
- **Muscle contraction**
- **Glandular secretion**

*PTH acts to keep this concentration constant.*
Laboratories routinely measure total calcium conc. (that is both the **bound and unbound** fractions) in a serum sample. If albumin conc. falls, total serum calcium become low because the bound fraction is decreased.

Adjusted calcium (mmol/L) = Total Ca + 0.02(47 - alb.)
Hypocalcaemia

Etiology

The causes of hypocalcaemia include:

- Vitamin D deficiency
- Hypoparathyroidism
- Magnesium deficiency
Renal disease

The diseased kidneys fail to synthesize 1,25-DHCC. Increased PTH secretion in response to the hypocalcaemia may lead to bone disease if untreated.
Pseudohypoparathyroidism;
PTH is secreted but there is failure of target tissue receptors to respond to the hormone.

Hungry bone syndrome;
There can be severe and potentially fatal hypocalcaemia with accompanying hypophosphataemia after parathyroectomy, due to rapid remineralization of bone (after sudden decrease in PTH).

Rarer causes such as;
Malignancy, acute rhabdomyolysis, acute pancreatitis, ethylene glycol poisoning or bone marrow transplantation.
Clinical features
The clinical features of hypocalcaemia include;
Neurological features such as tingling, tetany, and mental changes;
Cardiovascular signs such as an abnormal ECG; and cataracts.
Treatment

The management calls for the treatment of the cause of the hypocalcaemia, if this is possible. Oral calcium supplements are commonly prescribed in mild disorders, 1,25 DHCC or the synthetic vitamin D metabolite 1α hydroxycholecalciferol, can be given.
Hypercalcaemia

Clinical features

Symptoms of hypercalcaemia include;

• Neurological and psychiatric features such as lethargy, confusion, irritability and depression.
• Gastrointestinal problems such as anorexia, abdominal pain, nausea, vomiting, and constipation.
• Renal features such as thirst and polyuria, and renal calculi.
• Cardiac arrhythmias.
Diagnosis

The commonest causes of hypercalcaemia are primary hyperparathyroidism and malignancy.

Primary hyperparathyroidism is most often due to a single parathyroid adenoma, which secretes PTH independently of feedback control by plasma calcium.

Hypercalcaemia associated with malignancy is the commonest cause of a high calcium.
Treatment

Treatment is urgent if S. Ca ions more than 3.5 mmol/L; the priority is to reduce it to safe level. Intravenous saline is administered first to restore the glomerular filtration rate and promote a diuresis. Although steroids, methramycin, calcitonin and intravenous phosphate have been used.
Phosphate

Phosphate is abundant in the body and is an important intracellular and extracellular anion. Much of the phosphate inside cells is covalently attached to lipids and proteins. Phosphorylation and dephosphorylation of enzymes are important mechanisms in the regulation of metabolic activity. Most of the body's phosphate is in bone (17 mmol in bone, 3000 mmol in soft tissue, and only 1 mmol/L in plasma). Phosphate changes accompany calcium deposition and resorption of bone. Control of ECF phosphate concentration is achieved by the kidney, where tubular reabsorption is reduced by PTH.
Plasma inorganic phosphate

At physiological hydrogen concentrations, phosphate exists in the ECF both as monohydrogen phosphate and as dihydrogen phosphate. Both forms are together termed ‘phosphate’ and the total is normally maintained within the limits 0.8-1.4 mmol/L.
Hypophosphataemia

Severe hypophosphataemia (<0.3 mmol/L) is rare and causes muscle weakness, which may lead to respiratory impairment.

Causes of a low serum phosphate include:

• Hyperparathyroidism, the effect of a high PTH is to increase phosphate excretion by the kidneys and this contributes to a low serum concentration.
• Treatment of diabetic ketoacidosis. The effect of insulin in causing the shift of glucose into cells may cause similar shifts of phosphate, which may result in hypophosphataemia.

• Alkalosis. Especially respiratory, due to movement of phosphate into cells.

• Hungry bone syndrome

• Ingestion of non-absorbable antacids, such as aluminium hydroxide. These prevent phosphate absorption.

• Congenital defects of tubular phosphate reabsorption. In these conditions phosphate is lost from the body.
Hyperphosphataemia

Persistent hyperphosphataemia may result in calcium phosphate deposition in soft tissues. Causes of a high serum phosphate concentration include;

• Renal failure;
  phosphate excretion is impaired. This is the commonest cause of hyperphosphataemia.

• Hypoparathyroidism;
  The effect of a low circulating PTH decreases phosphate excretion by the kidneys, and this contributes to a high serum concentration.
• Redistribution;

Cell damage (lysis), eg. Hemolysis, tumor damage and rhabdomyolysis.

• Acidosis;

There is impaired metabolism and therefore decreased intracellular utilization of phosphate.

• Pseudohypoparathyroidism;

There is tissue resistance to PTH.
Magnesium (Mg)

Magnesium ions are the second most abundant intracellular cations, after potassium.

Magnesium is influences the secretion as well as action of PTH. Severe hypomagnesaemia may lead to hypoparathyroidism and refractory hypocalcaemia, which is usually easily correctable by magnesium supplementation.
Serum magnesium

Hypermagnaeaeemia is uncommon but is occasionally seen in renal failure.

Hypomagnaeaeemia is usually associated with deficient dietary intake.

The symptoms hypomagnaeaeemia are very similar to those of hypocalcaemia: impaired neuromuscular function such as tetany, hyperirritability, tremor, convulsions and muscle weakness.
Bone diseases

Osteomalacia and rickets

Osteomalacia is the name given to defective bone mineralization in adults. Rickets is characterized by defects of bone and cartilage mineralization in children.

In severe osteomalacia due to vitamin D deficiency, serum calcium will fall, and there will be an appropriate increase in PTH secretion. Serum alkaline phosphatase (ALP) will be activated.
Paget's disease

Paget's disease is common in the elderly and characterized by increased osteoclastic activity, which leads to increased bone resorption.

The clinical presentation is almost always bone pain, which can be particularly severe. Serum alkaline phosphatase (ALP) is high, and urinary hydroxyproline excretion is elevated. These provide a way of monitoring the progress of the disease.
Osteoporosis

Bone is in a constant state of turnover, which is kept in balance by opposing actions of osteoblasts (bone formation) and osteoclasts (bone resorption).

Osteoporosis results when, irrespective of the cause, this balance is disturbed and shifts in favour of resorption. It is defined as a progressive systemic skeletal disorder characterized by low bone mineral density (BMD), deterioration of the microarchitecture of bone tissue and susceptibility to fracture.
Risk factors

Age and menopause are the two main non-modifiable risk factors.

Contributing factors are genetic, dietary intake of calcium and vitamin D and physical exercise.

Other risk factors include history of previous fracture, family history of osteoporosis and hip fracture, sex hormone deficiency, smoking, alcoholism, immobility and sedentary lifestyle.
Diagnosis

Measurement of bone density by dual energy X-ray absorptiometry (DEXA) scan is the mainstay of diagnosis. Biochemical markers of bone turnover have very limited use in the diagnosis of osteoporosis
Principles of treatment

Treatment is aimed at strengthening the bone and preventing fractures.

The mainstay of drug treatment are oral bisphosphates that inhibit osteoclastic function, thereby slowing down bone loss.