Hypo-/Hypercalcemia

18

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18.1 Definition

Calcium (Ca) is a vital element of human physiology. It acts as an important regulator in numerous intracellular and extracellular processes within the human body including hormone release, transmitting nerve signals, muscle contraction, plasma coagulation, and enzyme regulation.

Almost all of body Ca is stored in bones. Plasma calcium levels are strictly regulated. Approximately 1 % of bone Ca is freely exchangeable with extracellular fluid and can be used to regulate plasma Ca balance.

Total plasma Ca levels in healthy individuals range from 2.20 to 2.60 mmol/l (8.8–10.4 mg/dl). Approximately 40 % of total plasma Ca is bound to plasma proteins mainly albumin. The remaining consists of ionized Ca and Ca complexed with phosphate and citrate. Ideally the ionized Ca should be determined as this is the physiologically active form.

A balanced dietary Ca intake, Ca absorption from GI tract in jejunum and proximal ileum, and renal Ca excretion help maintain the necessary calcium storage and plasma calcium concentration.

Kidneys filter approximately 270 mmol of calcium and must reabsorb more than 98 % of it to keep body's Ca levels in balance. The main renal reabsorption site is the proximal tubule.

Calcium and phosphate balance is dependent on parathyroid hormone (PTH), vitamin D, and calcitonin.

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Hypocalcemia is a decrease in total plasma calcium concentration below 2.20 mmol/l (8.8 mg/dl) in the presence of normal plasma protein concentration. The most common causes are hypoparathyroidism, idiopathic hypoparathyroidism, pseudoparathyroidism, vitamin D deficiency, renal tubular disease, hypoproteinemia, and hypomagnesemia.

Hypercalcemia is an increase in total plasma calcium concentration above 2.60 mmol/l (10.4 mg/dl). Excessive bone resorption resulting from increased PTH levels or malignancies with bone metastasis, excessive GI calcium absorption, Addison's disease, and prolonged treatment with thiazide diuretics are some of the most common causes.

18.2 Medical History

Medical history taking should start with a thorough questioning of previous illnesses that could cause hypo-/hypercalcemia. In addition patient's nutritional habits should be questioned in order to evaluate excessive or insufficient Ca intake. Regular daily medication should also be investigated as prolonged intake of certain medicines such as phenytoin, phenobarbital, rifampin, and furosemide or thiazide diuretics could alter Ca hemostasis. Irregularities in defecation such as diarrhea or obstipation are not just symptoms but can also manifest as causes for Ca balance disturbances.

18.3 Diagnostics

Diagnosis is established through measurement of blood calcium levels. Both hypo- and hypercalcemia especially in their mild state are mostly asymptomatic and often diagnosed accidentally during routine laboratory screening.

Clinical manifestations of hypocalcemia arise from neuromuscular irritability due to altered cellular membrane potential. Muscle cramps and mild/diffuse encephalopathy resulting in depression or dementia are some of the common symptoms. Prolonged hypocalcemia can lead to papilledema or cataracts. Severe hypocalcemia with Ca levels <1.75 mmol/l (<7 mg/dl) can manifest with tetany, laryngospasm, or generalized convulsions. Hyperventilation-induced tetany due to anxiety disorders should be taken into consideration as a possible differential diagnosis. Furthermore, arrhythmias can occasionally develop among severe cases. In ECG prolongation of QTc and ST intervals, T peaking, or T inversion can be observed. In chronic hypocalcemia, dry skin, coarse hair, and brittle nails can be seen. Candida infections occasionally occur especially in patients with idiopathic hypoparathyroidism.

PTH deficiency or absence causes hypoparathyroidism. This is almost always accompanied with hypocalcemia and hyperphosphatemia and is often associated

with tetany. Hypoparathyroidism could be a result of accidental removal of parathyroid glands during thyroidectomy or operation on the parathyroid gland itself. If PTH levels are undetectable, idiopathic parathyroidism should be taken into consideration as the cause. This is a rare condition that can occur sporadically or be inherited and is characterized with atrophy or absence of parathyroid glands. It manifests as an early onset during childhood and may be associated with Addison's disease.

Pseudoparathyroidism is a group of disorders resulting not from a PTH deficiency but target organ resistance to it. Type 1 pseudoparathyroidism manifests itself with hypocalcemia and normal or even elevated levels of PTH. These patients fail to present normal renal response to PTH and lack phosphaturia. The diagnosis of Type 2 pseudoparathyroidism requires the exclusion of vitamin D deficiency.

In patients with osteomalacia, plasma phosphate levels are mildly reduced and alkaline phosphatase is elevated. In order to distinguish between vitamin D deficiency from vitamin D-dependent states, hydroxycholecalciferol and calcitriol levels should be measured.

Clinical manifestations of hypercalcemia are constipation, nausea, vomiting, abdominal pain, ileus, polyuria, nocturia, and polydipsia. In severe cases confusion, delirium, psychosis, and coma can occur. Neuromuscular involvement may result in skeletal muscle weakness. Hypercalciuria (urinary calcium excretion greater than 4 mg/kg/day) is the most common abnormality identified in calcium stone formers. Hypercalcemia may also cause reversible acute renal failure or irreversible renal damage due to precipitation of Ca salts in kidney parenchyma (nephrocalcinosis). In severe hypercalcemia, a shortened QT interval is observed on ECG; cardiac arrhythmias may also occur. Hypercalcemia with Ca levels greater than 4.50 mmol/l (18 mg/dl) can result in renal failure, shock, and death.

Primary hyperparathyroidism is a common cause of hypercalciuria and is often associated with nephrolithiasis. It manifests with hypercalcemia, hypophosphatemia, and excessive bone resorption. In hospitalized patients, on the other hand, immobilization with prolonged bed rests such as after orthopedic or spinal surgeries can cause hypercalcemia due to accelerated bone resorption. Malignancy-associated hypercalcemia is another common cause of hypercalciuria in hospitalized patients. Tumors produce PTH-related protein (PTHrP) which over humoral pathways activates osteoclasts and results in bone lysis and hence hypercalcemia.

Many granulomatous diseases are known to cause hypercalcemia including tuberculosis, sarcoidosis, histoplasmosis, etc. Sarcoidosis is commonly associated with urolithiasis.

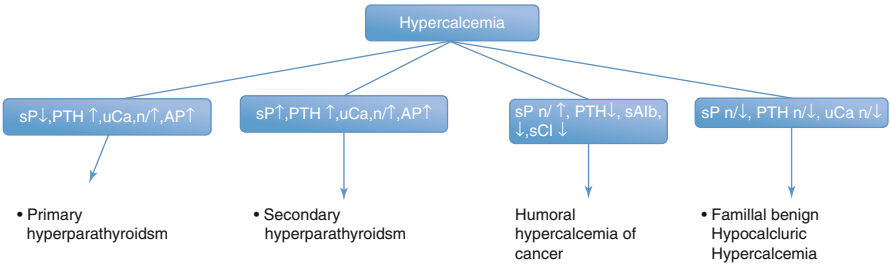
Besides medical history and clinical findings, radiographic evidence of bone disease may also help diagnose underlying cause of hypercalcemia.

Familial hypocalciuric hypercalcemia is a syndrome defined by the presence of hypermagnesemia and hypercalcemia without excessive renal calcium excretion. These patients normally do not develop nephrolithiasis.

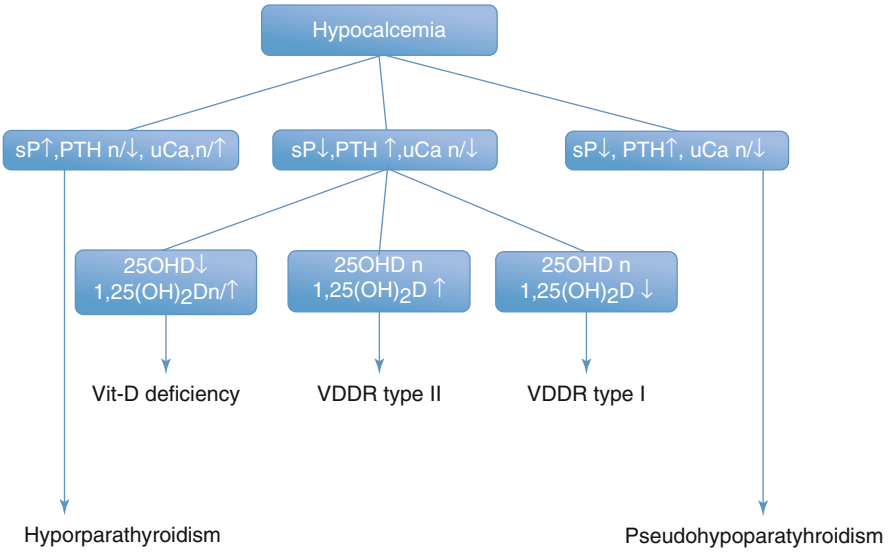
18.4 Differential Diagnosis

Hypocalcemia	Hypercalcemia
Hypoparathyroidism	Hyperparathyroidism
Pseudohypoparathyroidism	Malignant tumors
Vitamin D deficiency	Vitamin D toxicity
Renal tubular disease	Hyperthyroidism
Renal failure	Sarcoidosis
Magnesium depletion	Addison's disease
Acute pancreatitis	Pheochromocytoma
Hungry bone syndrome	Immobilization
Septic shock	Lithium intoxication
Hyperphosphatemia	Primary increase in 1, 25(OH)2D
Furosemide intake	Thiazide intake Paget disease

18.5 Diagnostic Work Flow



P Phosphate, PTH Parathyroid hormone, Ca Calcium, AP Alkaline Phosphatase,Alb Albumin, Cl Chloride, s Serum levels, n normal



P Phosphate, PTH Parathyroid hormone, Ca Calcium, 25OHD hydroxycholecalciferol, 1.25(OH)2D Calcitriol, s Serum levels, n normal, VDDR Vitamin D Dependent Rickets