**Electrolyte quintet**

# Calcium

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**Abnormalities in serum calcium concentration may have profound effects on neurological, gastrointestinal, and renal function. Maintenance of the normal serum calcium is a result of tightly regulated ion transport by the kidney, intestinal tract, and bone, mediated by calcaemic hormones especially parathyroid hormone and 1,25-dihydroxyvitamin $D_3$. Abnormalities in calcium transport that result in uncompensated influx into, or efflux from, the extracellular fluid, will result in hypercalcaemia or hypocalcaemia, respectively. When possible the biologically important ionised calcium concentration should be measured. A variety of common disorders are responsible for abnormalities in the serum calcium. Treatment of both hypercalcaemia and hypocalcaemia is dependent on the underlying disorder, the magnitude of the deviation of the serum calcium, and the severity of symptoms. Fortunately, in the case of hypercalcaemia, there is a broad selection of effective medications, especially the bisphosphonates. Treatment of hypocalcaemia relies on the provision of calcium and often vitamin D. In this article we review the mechanisms responsible for abnormalities in calcium homoeostatisis, the differential diagnosis of hypercalcaemia and hypocalcaemia, and appropriate therapy.**

## Calcium homoeostasis

Maintenance of normal serum calcium concentration in the extracellular fluid (ECF) depends on integrated regulation of calcium fluxes with respect to the intestinal tract, kidneys, and bone.[1,2] The precise regulation of serum is controlled by calcium itself, through a calcium-receptor first described in 1993,[3,4] and several hormones, the most important of which are parathyroid hormone (PTH) and 1,25-dihydroxyvitamin $D_3$ ($1,25(OH)_2D_3$).[5–7]

Intestinal calcium absorption is enhanced by $1,25(OH)_2D_3$. Over 98% of total body calcium is present in bone, of which about 1% appears to be freely exchangeable with ECF through both physicochemical and cell-mediated mechanisms. Both $1,25(OH)_2D_3$ and PTH stimulate the bone-resorbing osteoclasts, promoting calcium release into the ECF. PTH also stimulates renal hydroxylation of $25(OH)D_3$ to $1,25(OH)_2D_3$ and distal renal tubular calcium reabsorption.[5,6]

Calcium circulates in the ECF in three distinct fractions: about 50% is the biologically important ionised fraction, 40% is protein-bound and is not filterable by the kidney, and 10% is complexed to anions such as bicarbonate, citrate, sulphate, phosphate, and lactate. Most of the protein-bound calcium is bound to albumin, the remainder being complexed to globulins. Disorders that lower serum albumin will lower total serum calcium but have a lesser effect on the ionised calcium concentration. In general each 1 g/dL of albumin binds about 0·2 mmol/L (0·8 mg/dL) of calcium so to correct for hypoalbuminaemia 0·2 mmol/L must be added to the total calcium concentration for each 1 g/dL decrease in albumin concentration from the normal 4·0 g/dL.[5,6,8,9]

Binding of calcium to albumin is also affected by ECF pH. Acidaemia will decrease protein binding and increase the ionised calcium.[8] For each 0·1 decrease in pH ionised calcium rises by about 0·05 mmol/L.

These corrections for albumin and pH are poor substitutes for measuring ionised calcium. Most clinical laboratories can readily measure this biologically important fraction, and ionised calcium should be used whenever possible to guide therapy. In this review "serum calcium" refers to total calcium because the transition to measuring ionised calcium only is slow.

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Panel 1: **Common causes of hypercalcaemia**

| | |
|---|---|
| Hyperparathyroidism | Thyrotoxicosis |
| Malignancy | Vitamin intoxication |
| Thiazide diuretics | Renal failure |
| Immobilisation | Renal transplantation |
| Granulomatous disease | Milk-alkali syndrome |
| Familial hypocalciuric hypercalcaemia | |

## Hypercalcaemia

Hypercalcaemia occurs when calcium influx into the ECF from the intestine and/or bone exceeds the efflux to intestine, bone, and/or kidney. This generally happens when the influx of calcium from bone or the intestine exceeds renal calcium excretory capacity. For example, an influx of calcium from bone may occur in the setting of malignancy or increased PTH while an influx from the intestine may arise during hypervitaminosis D, secondary to excess intake or to a granulomatous disorder such as sarcoid.[6,9–11]

## Symptoms of hypercalcaemia

The symptoms associated with hypercalcaemia generally correlate with the magnitude and rapidity of the rise in serum calcium. Mild hypercalcaemia (figure), often observed with primary hyperparathyroidism, is generally asymptomatic.[11,12] More severe hypercalcaemia is frequently associated with symptoms, neurological, gastrointestinal, and renal. The neurological manifestations range from mild drowsiness, progressing to weakness, depression, lethargy, stupor, and coma; gastrointestinal symptoms may include constipation, nausea, vomiting, anorexia, and peptic ulcer disease;

**Glossary and abbreviations**

| | |
|---|---|
| 1 mmol/L (calcium) | 4 mg/dL |
| 1 mg/dL (calcium) | 0·25 mmol/L |
| ECF | Extracellular fluid |
| GFR | Glomerular filtration rate |
| $1,25(OH_2)D_3$ | 1,25-dihydroxyvitamin $D_3$ |
| PTH | Parathyroid hormone |
| PTHrP | PTH-related peptide |

hypercalciuria-induced nephrogenic diabetes insipidus often results in polyuria leading to ECF volume depletion and a reduction in the glomerular filtration rate (GFR), which may lead to a further increase in calcium concentration. Hypercalcaemia may also result in nephrolithiasis, nephrocalcinosis, and potentiation of digitalis toxicity.[6,9,11,13]

## Differential diagnosis of hypercalcaemia

Primary hyperparathyroidism is the leading cause of hypercalcaemia (panel 1), accounting for more than 50% of patients. Often the patients are elderly females who are found to have a benign adenoma of a single parathyroid gland; parathyroid carcinoma is very rare. The excess PTH leads to a direct increase in renal calcium reabsorption, an increase in serum $1,25(OH)_2D_3$ increasing intestinal calcium absorption, and an increase in bone turnover with resorption predominating over formation. Primary hyperparathyroidism is generally diagnosed by finding an inappropriately raised intact PTH with a mildly increased serum calcium concentration and normal renal function.[6,11,13] Up to 6% of patients with calcium-containing kidney stones have hyperparathyroidism. In these patients the increased filtered load of calcium exceeds the increased renal reabsorption, leading to hypercalciuria and renal stone formation. With the advent of routine measurement of serum calcium, hypercalcaemia and the causative hyperparathyroidism are often diagnosed and treated before stones form.

Malignancy is the second leading cause of hypercalcaemia and may be related to direct bone destruction or secretion of calcaemic factor(s) by malignant cells.[14,15] Patients with squamous-cell lung cancer and metastatic carcinoma of the breast are most prone to hypercalcaemia while others with myeloma, T-cell tumours, renal-cell carcinoma, and other squamous-cell tumours are also at risk. Many tumours produce PTH-related peptide (PTH-rP) which binds to PTH receptors yet is not detected on standard PTH assays; specific assays for PTH-rP are available.[16] In general the malignancy is already evident when patients present with hypercalcaemia.

Thiazide diuretics increase renal calcium reabsorption, which resolves with discontinuation of the medication. Immobilisation, notably in younger patients, may lead to a rapid increase in bone resorption and hypercalcaemia especially in the presence of renal insufficiency.

Granulomatous diseases such as sarcoidosis, tuberculosis, and leprosy may produce hypercalciuria and hypercalcaemia due to granulomatous tissue conversion of $25(OH)D_3$ to $1,25(OH)_2D_3$. Familial hypocalciuric hypercalcaemia is an autosomal dominant disorder which causes mild hypercalcaemia, modest hypophosphataemia, and reduced renal calcium excretion. The patients have a mutation in the calcium receptor causing a reduction in activity.[3,4] PTH levels are normal and parathyroidectomy is not indicated. Excess thyroid hormone stimulates osteoclastic bone resorption which may result in hypercalcaemia. Vitamin D intoxication in food or vitamin faddists and vitamin A excess can also cause hypercalcaemia.

Hypocalcaemia, not hypercalcaemia, is generally observed in patients with renal failure.[17] However, in hypercalcaemic patients one must determine if it was abnormal serum calcium that induced the renal failure, as occasionally happens in sarcoidosis, myeloma, immobilisation, and the milk-alkali syndrome. Hypercalcaemia may also be observed in the recovery phase of rhabdomyolysis-induced renal insufficiency as calcium recently deposited in muscle and soft tissues is mobilised.

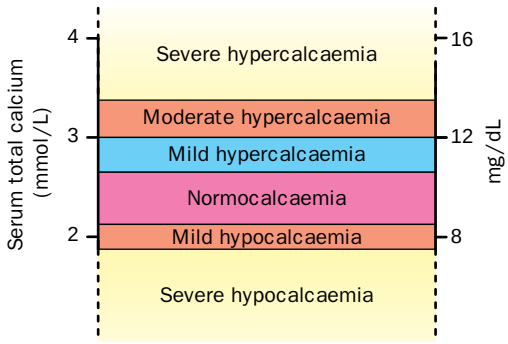
Hypercalcaemia may be observed during $1,25(OH)_2D_3$ replacement therapy in patients on dialysis, especially if they are taking oral calcium as a phosphorus binder or are being dialysed against a high calcium bath. Dialysis patients may have aluminium intoxication which also predisposes them to hypercalcaemia. Some renal patients may develop severe secondary hyperparathyroidism with marked hyperplasia of the parathyroid glands and subsequent hypercalcaemia. If patients with parathyroid hyperplasia then receive a renal transplant, PTH secretion continues and hypercalcaemia may develop or worsen. The hypercalcaemia tends to decrease over the ensuing 6–12 months as the hypertrophied parathyroid glands involute.

Consumption of large amounts of calcium-containing non-absorbable antacids may lead to hypercalcaemia, alkalaemia, nephrocalcinosis, and renal insufficiency. This uncommon disorder, termed milk-alkali syndrome, may become more prevalent as use of calcium and alkali preparations is increasing in efforts to prevent and treat osteoporosis.

Panel 2: **Indications for surgery in asymptomatic primary hyperparathyroidism[12]**

Raised serum calcium (>2·85 mmol/L or 11·4 mg/dL)*
History of episode of life-threatening hypercalcaemia
Reduced creatinine clearance (<70% of that for age-matched healthy people)*
Kidney stone(s)
Raised 24 h urinary calcium excretion (>100 μmol or 400 mg)*
Substantial reduction of bone mass (>2 SD below mean for age,sex, and ethnic group)*

*Generally accepted examples in parentheses)




**Normal range for serum calcium**

## Treatment of hypercalcaemia

Rational therapy depends on the severity of the hypercalcaemia (figure) and on its cause. General measures aimed at lowering the serum calcium should be applied to hypercalcaemic outpatients. Whenever possible, medications known to cause or worsen hypercalcaemia, such as thiazide diuretics, should be discontinued and immobilisation avoided. Generous oral salt and water intake should be maintained not only to

promote calcium excretion but also to avoid ECF volume depletion, which would exacerbate hypercalcaemia.[11,18]

### *Mild hypercalcaemia*

Most cases of mild hypercalcaemia are caused by primary hyperparathyroidism.[11] Management of asymptomatic patients remains controversial.[12] To qualify for medical, and avoid surgical, management these patients should have, besides only a mild increase in serum calcium, no previous episodes of life-threatening hypercalcaemia and normal renal function and bone density. These patients must be monitored closely with frequent questioning about symptoms, measurement of blood pressure, serum calcium, renal function, and possibly urinary calcium excretion, abdominal radiographs, and measurements of bone density. Specific indications for surgery in asymptomatic patients with primary hyperparathyroidism are listed in panel 2.[12] All symptomatic patients with primary hyperparathyroidism should be promptly referred to a surgeon specialising in the parathyroid.

20 patients with primary hyperparathyroidism were given short-term treatment with the calcium-receptor agonist R-568.[19] The agonist caused a dose-dependent inhibition of parathyroid secretion and, at the highest doses tested, decreased serum ionised calcium. Determination of the role of such agents requires long-term trials.

Immediate intervention directed at the mild hypercalcaemia itself is not usually necessary. In recently postmenopausal women, oestrogen deficiency has been implicated in the pathogenesis of primary hyperparathyroidism, and here oestrogen replacement will reduce serum calcium (0·125–0·25 mmol/L) with a concomitant reduction of urinary calcium but not PTH.[11,20] Oestrogen replacement also protects against bone loss and cardiovascular morbidity.

In outpatients with mild primary hyperparathyroidism all diuretics should be avoided. Loop diuretics such as furosemide increase urine calcium excretion but may also induce ECF volume depletion, increasing renal calcium resorption and worsening the hypercalcaemia. Thiazides are contraindicated because they reduce urine calcium excretion and increase the serum calcium. While phosphorus will coprecipitate with calcium, the resulting ectopic calcification damages kidneys, blood vessels, and soft tissues.[11,18]

Bisposphonates lower serum calcium but they are rarely required in mild hypercalcaemia. Alendronate sodium is an oral bisphosphonate used for treatment of osteoporosis. It is not licenced for hypercalcaemia but its known side-effect of mild hypocalcaemia might warrant such use, if clinical trials demonstrate efficacy.

### *Moderate hypercalcaemia*

Patients with moderate hypercalcaemia (figure) are more likely to have symptoms. Treatment decisions depend on the severity of the symptoms, which generally correlate with the rate of rise of the serum calcium. In patients with few or mild symptoms, treatment of the underlying disorder may decrease serum calcium before symptoms become serious. When neurological symptoms are the sole manifestation of hypercalcaemia, other reasons for the altered mental status changes must be excluded before the symptoms are attributed to the raised serum calcium.[10,11]

If gastrointestinal or neurological symptoms are severe it may be difficult simply to provide oral salt and water, and intravenous normal saline may be required to restore intravascular volume, leading to improved GFR and enhanced renal calcium excretion. As the serum calcium falls the renal tubular concentrating mechanism will improve, so stabilising intravascular volume.[6,9–11,13] Gentle hydration with intravenous saline may be enough but if congestive heart failure ensues or if more rapid lowering of serum calcium is desired, a loop diuretic will enhance calcium excretion. ECF volume depletion must be avoided because this will worsen hypercalcaemia. In a setting of renal insufficiency, higher doses of loop diuretics are needed. Thiazide diuretics must be avoided. Intravenous saline plus a loop diuretic should decrease the serum calcium rapidly, usually by 0·25–0·75 mmol/L in 1 or 2 days.[6,10,11,13] If this reduction is insufficient bisphosphonate may be required.

### *Severe hypercalcaemia*

A serum calcium level above 3·375 mmol/L (13·5 mg/dL) generally constitutes an emergency, warranting aggressive intervention whether there are symptoms or not. The patient should be treated by a combination of measures enhancing volume repletion and renal calcium excretion, reducing bone resorption, and targeting the underlying disease process.[10,13,15,21] Patients with a raised PTH should be referred for urgent parathyroidectomy. However, malignancy is the usual reason for severe hypercalcaemia. Initial treatment for the hypercalcaemia is with intravenous normal saline and a loop diuretic, as aggressively as the patient's cardiovascular status will allow. Monitoring of haemodynamic and electrolyte status is necessary, ideally in an intensive-care unit. With intravenous hydration and a loop diuretic the serum calcium will fall rapidly yet still be insufficient, and the effect lasts only as long as the infusion and diuresis continue. Since osteoclast activity is usually enhanced, measures directed at reducing bone resorption should be initiated at the same time,[6,10,13] using a bisphosphonate or other agent.

### *Bisphosphonates*

Bisphosphonates, analogues of pyrophosphate, have become the principal class of agent for the management of hypercalcaemia due to enhanced osteoclastic bone resorption.[22–24] They bind firmly to bone mineral and since they are resistant to enzymatic breakdown by phosphatases they have a very long half-life. Intravenous administration in large volumes of fluid (500 mL or more) over at least 4 h is recommended because precipitated calcium bisphosphonate carries the risk of nephrotoxicity.[10] In patients with renal insufficiency, a cautious trial of lower doses diluted in larger volumes of fluid may be attempted, the dose being raised if renal function remains stable.

With etidronate (7·5 mg/kg daily over 4 h for 3–7 days) the serum calcium begins to fall by day 2 and reaches a nadir on about day 7; the hypocalcaemic effect may last for weeks. Normal calcium levels will be achieved in most patients given a 7-day course and in 30–40% with the 3-day course of therapy. Therapy should be interrupted if the serum calcium drops too quickly (eg, by 0·5 mmol/L [2 mg/dL] or more) within the first 2–3 days becuse hypocalcemia should be avoided.[16] With short-term use, etidronate may cause a transient rise in serum creatinine but otherwise the drug is well-tolerated. Chronic therapy

may lead to osteomalacia.[13]

Pamidronate is more potent than etidronate. The serum calcium will almost always fall to normal one week after a single 90 mg dose and normocalcaemia may persist for a month. A single 60 mg dose over 4 h is generally adequate where the serum calcium is below 3·38 mmol/L (13·5 mg/dL), 90 mg being reserved for more severe hypercalcaemia.[10] Pamidronate does not appear to worsen renal function, even in patients with severe renal insufficiency, when infused over several hours.[10,25]

Clodronate (4–6 mg/kg daily over 2–4 h) is an effective bisphosphonate to lower serum calcium. It is widely used in Europe but is not available in the USA. Alendronate, which also lowers serum calcium when given intravenously, is licensed only as oral therapy for osteoporosis.

### *Other agents*

Plicamycin (mithramycin) inhibits osteoclastic RNA synthesis and decreases bone resorption. It will lower the serum calcium more quickly than bisphosphonates do but significant side-effects (raised transaminases, nephrotoxicity with proteinuria, thrombocytopenia, nausea, and local inflammation or cellulitis at sites of extravasation) decrease enthusiasm for this agent unless the calcium concentration needs to be lowered very rapidly.[10,13]

Calcitonin inhibits osteoclastic bone resorption and enhances renal calcium excretion. The hypocalcaemic effect begins within hours, with a nadir in serum calcium within 12–24 h, but the effect on calcium concentrations is modest and transient, and calcitonin alone has no place in the treatment of severe hypercalcaemia. However, in very severe cases, it is an excellent addition to the later-acting plicamycin or bisphosphonates.[10,13]

Gallium nitrate binds to bone mineral and reduces hydroxyapatite crystal solubility. As with bisphosphonates, it takes several days before a nadir in serum calcum is reached, and this lasts about a week. Side-effects are frequent and severe, with nephrotoxicity, hypophosphataemia, and anaemia. The drug should be avoided in patients with renal insufficiency or those receiving another nephrotoxic agent.

Glucocorticoids are effective in hypercalcaemia associated with haematological malignancy (lymphoma, multiple myeloma) and in diseases related to $1,25(OH)_2D_3$ excess, such as sarcoidosis and vitamin D toxicity.[10,11]

Haemodialysis against low-calcium dialysate is more effective than peritoneal dialysis for the dialysis-dependent hypercalcaemic patient.

## Hypocalcaemia

Hypocalcaemia occurs when there is a nett efflux of calcium from the ECF—ie, calcium is lost from the ECF, often through renal mechanisms, in greater quantities than can be replaced by the intestine or bone. Falsely low levels of calcium due to hypoalbuminaemia should be excluded by measuring ionised calcium.

### *Symptoms of hypocalcaemia*

As with hypercalcaemia, the symptoms generally correlate with the magnitude and rapidity of the fall in serum calcium. Manifestations of neuromuscular irritability predominate, and include paraesthesiae of the distal extremities and circumoral area, Chvostek and Trousseau signs, muscle cramps, laryngospasm, tetany, and seizures. The Chvostek sign, which is present in some normocalcaemic individuals, is a facial twitch elicited by tapping on the facial nerve just below the zygomatic bone with the patient's mouth slightly open.[6,26] The Trousseau sign is induced by brachial artery occlusion with a sphygmomanometer cuff inflated above the systolic blood presure for 3 min. The resultant wrist and metacarpophalangeal joint flexion, hyperextended fingers, and flexion of the thumb on to the palm are specific for hypocalcaemia. Dementia and movement disorders, if present during hypocalcaemia, may improve with normalisation of serum calcium. Cardiac manifestations consist of a prolonged QT interval which may progress to ventricular fibrillation or heart block.[6,26]

Panel 3: **Common causes of hypocalcaemia**

| | |
|---|---|
| Hypoparathyroidism | Following parathyroidectomy |
| Pseudohypoparathyroidism | Hypomagnesaemia |
| Malignant disease | Acute pancreatitis |
| Rhabdomyolysis | Septic shock |
| Chronic renal insufficiency | Vitamin D deficiency |

## Differential diagnosis of hypocalcaemia

Causes of hypocalcaemia are listed in panel 3. In idiopathic or postoperative hypoparathyroidism a deficiency of PTH leads to increased renal calcium excretion and decreased intestinal calcium absorption, the latter secondary to reduced $1,25(OH)_2D_3$ production. Pseudohypoparathyroidism is a rare hereditary disorder affecting the target-cell response to PTH; the PTH is raised but in most such patients cyclic AMP fails to respond to PTH. The patients also commonly have shortened metacarpals and metatarsals besides short stature, obesity, and heterotopic calcification.

Patients with malignant disease often have a decrease in serum albumin, leading to a fall in total (but not ionised) calcium. Malignancies such as prostate and breast cancer increase osteoblastic activity leading to increased bone formation and hypocalcaemia. Rapid cell destruction in response to chemotherapy ("tumour-lysis syndrome"), will increase serum phosphorus, leading to complexation with serum calcium and hypocalcaemia. Trauma, especially with rapid crush injuries to major muscle groups causing rhabdomylosis, releases cellular phosphorus, again complexing with calcium and lowering serum calcium.

During renal insufficiency phosphorus excretion is reduced, with continued intestinal phosphorus absorption, resulting in hyperphosphataemia.[17] The increased serum phosphorus down-regulates the 1α-hydroxylase responsible for the renal conversion of $25(OH)D_3$ to $1,25(OH)_2D_3$ and the decrease in renal mass itself decreases $1,25(OH)_2D_3$ production, resulting in reduced intestinal calcium absorption and hypocalcaemia. Surgical reduction of the excess parathyroid mass in patients with secondary or tertiary hyperparathyroidism often results in profound hypocalcaemia as bone is being remineralised. This "hungry bone syndrome" may require prolonged, substantial calcium replacement.

Hypocalcaemia and hypomagnesaemia frequently coexist and are often due to decreased absorption of dietary divalent cations or to poor dietary intake.

Hypomagnesaemia impairs PTH secretion and may interfere with its peripheral action. Pancreatitis leads to the release of pancreatic lipase, degradation of retroperitonal omental fat, and binding of calcium in the peritoneum—and this loss of extracellular calcium results in hypocalcaemia. Hypomagnesemia and hypoalbuminaemia also have been reported to contribute to the hypocalcaemia of acute pancreatitis.

Endotoxic shock is associated with hypocalcaemia through unknown mechanisms. Since myocardial contraction is correlated directly with ionised calcium concentration, the hypocalcaemia may be responsible, in part, for hypotension.

Dietary deficiency of vitamin D will be uncommon where, as in the USA, it is added to dairy products. This fat-soluble vitamin is subject to malabsorption, and levels may be low in chronic liver disease and primary biliary cirrhosis. As discussed, renal failure also decreases levels of $1,25(OH)_2D_3$ and some anticonvulsant drugs increase the turnover of vitamin D into inactive compounds, resulting in a decrease in serum levels of $1,25(OH)_2D_3$.

## Treatment of hypocalcaemia

As with hypercalcaemia, rational therapy depends on the severity of the hypocalcaemia and its cause. While treatment generally begins with administration of calcium, the form of calcium and the need for additional agents such as vitamin D depends on the acuity and severity of the hypocalcaemia as well as the underlying cause. Patients with symptomatic hypocalcaemia or those with corrected serum levels of 1·875 mmol/L (7·5 mg/dL) or less should be treated with parenteral calcium until the symptoms cease or the calcium concentration rises above this point.[27–29] Chronic, asymptomatic mild hypocalcaemia is usually treated with oral calcium supplements.[6,9,26] Since calcium binds with dietary phosphate and oxalate to form insoluble and unabsorbable salts, calcium is better absorbed when taken between meals. PTH is not available for clinical use so patients with little or no PTH are usually treated with calcium and vitamin D.

Several general principles apply to the management of a hypocalcaemic patient. The magnesium level should be checked and, if low, corrected. In a setting of sepsis or renal failure, metabolic acidosis may accompany hypocalcaemia and calcium must be replaced before the acidosis is corrected. Calcium and hydrogen ions compete for protein-binding sites so an increase in pH with alkali therapy will increase the binding sites for calcium, leading to a rapid fall in ionised calcium, potentially resulting in cardiac arrest—unless the calcium is corrected first. Sodium bicarbonate and calcium salts must be infused in separate lines to avoid precipitation of calcium carbonate. In renal failure, haemodialysis against a high calcium, high bicarbonate bath safely and rapidly corrects both conditions. Patients on digoxin should be monitored carefully because administration of calcium may potentiate digitalis toxicity and cause death.

Patients with hypoparathyroidism have decreased renal calcium reabsorption. Oral calcium supplementation, especially with concomitant vitamin D administration, increases the filtered load of calcium and results in hypercalciuria with possible nephrocalcinosis or nephrolithiasis. In this setting serum calcium levels should be maintained at the lower limit of normal with 24 h urinary calcium excretion kept below 1 mmol/kg (4 mg/kg). Thiazide diuretics increase renal calcium reabsorption and may be useful in patients with hypoparathyroidism.

Hyperphosphataemia may accompany hypocalcaemia in patients with hypoparathyroidism, renal dsease, rhabdomyolysis, and tumour lysis. To avoid soft-tissue calcium phosphate precipitation, calcium supplementation should be accompanied by oral phosphorus binders and, if possible, calcium supplementation should be delayed until the serum phosphate has fallen below 1·5 mmol/L (6 mg/dL).

### *Acute hypocalcaemia*

In acute symptomatic hypocalcaemia there is a rapid decrease in serum calcium associated with signs and symptoms of hypocalcaemia. Generally this happens at concentrations of 1·875 mmol/L (7·5 mg/dL) or less and warrants rapid parental administration of calcium. Infusion of 15 mg/kg (3·75 mmol/kg) of elemental calcium over 4–6 h will raise the total serum calcium by 0·5–0·75 mmol/L (2–3 mg/dL).[26] There are several forms of calcium for intravenous administration.

Calcium gluconate (10%) is available in 10 mL ampoules containing 94 mg of elemental calcium. In emergency situations, one ampoule may be infused directly over 4 min followed by a calcium gluconate drip.[30] Solutions with more than 200 mg calcium per 100 mL (more than two ampoules of calcium gluconate per 100 mL) should be avoided because calcium is irritating to veins and, if extravasated, to soft tissues too. Ten ampoules may be combined with 900 mL 5% dextrose to form a 940 mg/L solution to be infused at 50 mL/h (47 mg calcium) to start with, the rate then being titrated. If necessary, this solution may be infused as rapidly as over 4 to 6 h.[6,26,30]

Calcium gluceptate (10%) is similar to calcium gluconate but is provided as 90 mg elemental calcium in 5 mL and is often useful in patients who cannot tolerate large volumes of fluid. Ten ampoules added to 450 mL 5% dextrose provides 900 mg calcium but only in 500 mL of fluid. Calcium chloride (10%) provides more calcium per ampoule (272 mg in 10 mL) and is more bioavailable than calcium given as the gluconate or gluceptate, so it results in a more rapid rise in serum calcium. However, calcium chloride is more toxic to veins than the other calcium preparations, making it less desirable for prolonged infusion. Calcium glubionate is an oral preparation providing 23 mg elemental calcium/mL. It is readly absorbed and well tolerated, making it an excellent supplement for infants and for adults lacking intravenous access.

Some patients, especially those on dialysis with hypocalcaemia after elective subtotal parathroidectomy, require emergency calcium and vitamin D therapy. After subtotal parathyroidectomy the marked decrease in PTH leads to calcium and phosphorus accumulation in the healing bone lesions and the fall in osteoclastic bone resorption followed by a sharp fall in serum calcium. The failed kidneys cannot increase production of $1,25(OH)_2D_3$ so intestinal calcium absorption remains low. Intravenous calcium is often required initially; however, on a chronic basis oral calcium supplements can be utilised with concomitant administration of $1,25(OH)_2D_3$. $1,25(OH)_2D_3$ is available in oral and intravenous preparations. Initially large intravenous doses are generally required (1·0–2·0 μg daily) decreasing to

maintenance oral daily doses or thrice weekly intravenous doses at dialysis of 0·25–1·0 μg.[26,30] Giving $1,25(OH)_2D_3$ and calcium for several days before subtotal parathyroidectomy may prevent extreme hypocalcaemia.

### *Chronic hypocalcaemia*

Treatment of chronic hypocalcaemia requires oral calcium to increase availability for intestinal absorption and, often, vitamin D to enhance absorption. Absorption will depend on the calcium preparation used and on the timing of ingestion. Treatment usually begins at a daily dose of 1000–2600 mg (250–650 mmol) divided into two, three, or four doses and taken between meals, the dose being adjusted according to follow-up calcium levels. Calcium carbonate is widely available in tablets containing 500–750 mg calcium. Calcium citrate is well absorbed but it enhances aluminium absorption and may predispose to aluminium toxicity in patients with renal insufficiency. Calcium glubionate is more expensive than tablets and is generally reserved for severe cases lacking intravenous access and for children. Calcium phosphate should be avoided because it may exacerbate hyperphosphataemia and metastatic calcification.[30,31]

When the hypocalcaemia is associated with insufficient vitamin D, replacement of the hormone is generally required. Oral $1,25(OH)_2D_3$ acts rapidly since it requires no further metabolism to function. 0·5–1·0 μg daily is usually sufficient though in extreme cases, such as immediately post-parathyroidectomy, larger doses may be required. Calcitriol is more expensive than the parent vitamin D compounds, vitamin $D_2$ (ergocalciferol), and vitamin $D_3$. Vitamins $D_2$ or $D_3$ are adequate to avoid nutritional deficiency at doses of 400 units a day or for malabsorption at higher doses (50 000–100 000 units). However, they require conversion to $1,25(OH)_2D_3$ for maximal biological action so they are no good where 25- or 1α-hydroxylation are impaired, as in liver and renal failure, hypoparathyroidism, and vitamin-D-dependent rickets type 1. In contrast to the rapid elimination of $1,25(OH)_2D_3$, vitamins $D_2$ and $D_3$ may continue to function for several weeks, potentially resulting in hypervitaminosis D.[6,30]

#### References


1 Bushinsky DA, Krieger NS. Integration of calcium metabolism in the adult. In: Coe FL, Favus MJ, eds. Disorders of bone and mineral metabolism. New York: Raven, 1992: 417–32.

2 Bushinsky DA, Krieger NS. Role of the skeleton in calcium homoeostasis. In: Seldin DW, Giebisch G, eds. The kidney: physiology and pathophysiology. New York: Raven, 1992: 2395–430.

3 Brown EM, Gamba G, Riccardi D, et al. Cloning and characterization of an extracellular Ca(2+)-sensing receptor from bovine parathyroid. *Nature* 1993; **366:** 575–80.

4 Brown EM, Pollak M, Seidman CE, et al. Calcium-ion-sensing cell-surface receptors. *N Engl J Med* 1995; **333:** 234–40.

5 Monk RD, Bushinsky DA. Pathogenesis of idopathic hypercalciuria. In: Coe FL, Favus MJ, Pak CYC, Parks JH, Preminger GM, eds. Kidney stones: medical and surgical management. Philadelphia: Lippincott-Raven, 1996: 759–72.

6 Sutton RAL, Dirks JH. Disturbances of calcium and magnesium metabolism. In: Brenner BM, Rector FC, eds. The kidney. Philadelphia: Saunders, 1996: 1038–85.

7 Monk RD, Bushinsky DA. Treatment of calcium, phosphorus and magnesium disorders. In: Brady H, Wilcox C, eds. Disorders of fluid, electrolyte and acid-base disorders. Philadelphia: Saunders (in press).

8 Broadus AE. Mineral balance and homeostasis. In: Favus MJ, ed. Primer on the metabolic bone diseases and disorders of mineral metabolism. Philadelphis: Lippincott-Raven, 1996: 57–63.

9 Bushinsky DA. Homeostasis and disorders of calcium and phosphorus concentration. In: Greenberg A, ed. Primer on kidney diseases. San Diego: Academic, 1998: 106–13.

10 Shane E. Hypercalcemia: pathogenesis, clinical manifestations, differential diagnosis, and management. In: Flavus MJ, ed. Primer on the metabolic bone diseases and disorders of mineral metabolism. Philadelphia: Lippincott-Raven, 1996: 177–81.

11 Bilezikian JP. Management of hypercalcemia. *J Clin Endocrinol Metab* 1993; **77:** 1445–49.

12 Complete Proceedings of the Consensus Development Conference. Diagnosis and management of asymptomatic primary hyperparathyroidism. *J Bone Miner Res* 1991; **6** (suppl 2): S1–S165.

13 Bilezikian JP. Management of acute hypercalcemia. *N Engl J Med* 1992; **326:** 1196–203.

14 Mundy GR, Guise TA. Hypercalcemia of malignancy. *Am J Med* 1997; **103:** 134–45.

15 Kovacs CS, MacDonald SM, Chik CL, Bruera E. Hypercalcemia of malignancy in the palliative care patient: a treatment strategy. *J Pain Symptom Management* 1995; **10:** 224–32.

16 Budayr AA, Nissenson RA, Klein RF, et al. Increased serum levels of a parathyroid-like protein in malignancy-associated hypercalcemia. *Ann Intern Med* 1989; **111:** 807–12.

17 Bushinsky DA. The contribution of acidosis to renal osteodystrophy. *Kidney Int* 1995; **47:** 1816–32.

18 Shane E. Medical management of asymptomatic primary hyperparathyroidism. *J Bone Miner Res* 1991; **6** (S2): S131–34.

19 Silverberg SJ, Bone HG, Marriott TB, et al. Short-term inhibition of parathyroid hormone secretion by a calcium-receptor agonist in patients with primary hyperparathyroidism. *N Engl J Med* 1997; **337:** 1506–10.

20 Marcus R. Etrogens and progestins in the management of primary hyperparathyroidism. *J Bone Miner Res* 1991; **6** (S2): S125–29.

21 Raue F, Pecherstorfer M. Drug therapy of hypercalcemia due to malignancy. *Rec Results Cancer Res* 1994; **137:** 138–60.

22 Body JJ, Coleman RE, Piccart M. Use of bisphosphonates in cancer patients. *Cancer Treat Rev* 1996; **22:** 265–87.

23 Singer FR, Minoofar PN, Bisphosphonates in the treatment of disorders of mineral metabolism. *Adv Endocrinol Metab* 1995; **6:** 259–88.

24 Fleisch H. Bisphosphonates. Pharmacology and use in the treatment of tumor-induced hypercalcemia and metastatic bone disease. *Drugs* 1991; **42:** 919–44.

25 Berenson JR, Lichtenstein A, Porter L, et al. Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. *N Engl J Med* 1996; **334:** 488–93.

26 Shane E. Hypocalcemia: pathogenesis, differential diagnosis, and management. In: Favus MJ, ed. Primer on the metabolic bone diseases and disorders of mineral metabolism. Philadelphia: Lippincott-Raven, 1996: 217–19.

27 Reber PM, Heath H III. Hypocalcemic emergencies. *Med Clin N Am* 1995; **79:** 93–106.

28 Tohme JF, Bilezikian JP. Hypocalcemic emergencies. *Endocrinol Metab Clin N Am* 1993; **22:** 363–75.

29 Reber PM, Heath H III. Hypocalemic emergencies. *Med Clin N Am* 1995; **79:** 93–106.

30 Pak CYC. Calcium disorders: hypercalcemia and hypocalcemia. In: Kokko JP, Tannen RL, eds. Fluids and electrolytes. Philadelphia: WB Saunders, 1990: 596–630.

31 Hruska KA, Connolly J. Hyperphosphatemia and hypophosphatemia. In: Favus MJ, ed. Primer on the metabolic bone diseases and disorders of mineral metabolism. Philadelphia: Lippincott-Raven, 1996: 238–45.