Calcium and phosphate testing

Introduction

Calcium and phosphate usually form part of a 'bone' profile of tests that also includes measurement of serum albumin and alkaline phosphatase levels. Most laboratories report total calcium concentration in serum. This is influenced in particular by serum albumin concentration, and the total calcium is therefore also adjusted for the serum albumin concentration (ACa = serum Ca + (0.02(40–alb) (g/litre))). However, the adjustment is an approximation which may be inaccurate, particularly at extreme albumin concentrations.

Calcium in serum is divided between complexed and ionized fractions, which can vary with blood pH, or in patients who have received large amounts of citrated blood, as citrate binds calcium. For this reason some laboratories also offer ionized calcium, although the adjusted calcium is used is most routine situations.

Alkaline phosphatase is included as the contribution from the bone isoenzyme to total alkaline phosphatase activity in serum can provide information about the original of abnormal calcium results.

Hypercalcaemia

In many situations hypercalcaemia will develop in a context of known disease and the cause will be apparent. In the acute situation immediate treatment is required for 'severe' hypercalcaemia, identification of the cause becoming the secondary aim. In most outpatient and not-urgent situations, however, a simple diagnostic approach based on parathyroid hormone measurement can identify the great majority of causes. As with other biochemical electrolyte disorders, the 'action limits' offered are only approximate guidance, as rate of change and clinical signs and symptoms are more important than absolute values (*Figure 1*).

Hypercalcaemia can be defined as serum calcium adjusted for the serum albumin concentration above the upper limit of the population reference interval, or approximately 2.60 mmol/litre, although ranges may differ slightly depending on method and population studies. It can be classified as mild (up to 3.00 mmol/litre), moderate (up to 3.40 mmol/litre) or severe (over 3.40 mmol/litre), although rate of change is more important than absolute values. Prolonged venous stasis for a tourniquet is often quoted as increasing measured serum calcium, although changes are minimal for short tourniquet times (less than 1 minute).

A clinical filter will identify predisposing situations including drug-induced causes, particularly thiazide diuretics, and specific clinical contexts.

Parathyroid hormone measurement will distinguish between the leading causes of hyperparathyroidism (primary or secondary to renal dysfunction) and is recommended as an initial test, although the speed with which this can be performed will vary between hospitals.

Serum phosphate and alkaline phosphatase levels can provide further information on the likely cause of hypercalcaemia (*Table 1*), although no pattern is specific to any one disease. Phosphate levels are often low in primary hyperparathyroidism because of the action of parathyroid hormone, and the alkaline phosphatase level may be raised in primary hyperparathyroidism, but may also be raised in metastatic malignancy and Paget's disease.

If the patient is not taking vitamin D, a suppressed parathyroid hormone level indicates a probable non-parathyroid cause, typically as a result of malignancy (lung, breast or haematological malignancy = 74%; head and neck, renal or prostate = 11%; other or unknown primary malig-

Table 1. Causes of hypercalcaemia in hospital practice

Chronic kidney disease	53%
Renal transplant	21%
Hypercalcaemia of malignancy	11%
Osteoporosis	7%
Primary hyperparathyroidism	4%
Diabetes, liver disease, Paget's disease	3%
Granulomatous disease	0.5%

Figure 1. Assessment of unexplained raised serum adjusted calcium (ACa).

Repeat within 1 week to confirm unless patient acutely unwell, value rising rapidly or ACa over 3.4 mmol/litre	
Assess symptoms	Lethargy or weakness
	Confusion, impaired mentation
	Anorexia, nausea, vomiting
	Constipation
	Polyuria or polydipsia
	Bone pain
Consider more common causes depending on clinical presentation	Primary hyperparathyroidism
	Hypercalcaemia of malignancy
	Kidney disease
	Vitamin D treatment
	Immobilization
Check serum phosphate, alkaline phosphatase and creatinine levels	
Assess urgency: ACa 2.65–3.0 mmol/litre	Request parathyroid hormone with repeat ACa measurement to classify as parathyroid or non-parathyroid cause
	Request erythrocyte sedimentation rate, serum electrophoresis and targeted imaging investigations depending on clinical presentation pending specialist assessment
ACa 3–3.4 mmol/litre and symptomatic, or ≥3.5 mmol/litre	Urgent management required

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nancy = 15%). In the absence of clinical pointers a full blood count, renal and hepatic profiles, plasma erythrocyte sedimentation rate (or viscosity) and serum and urine protein electrophoresis are helpful immediate tests.

One rarer diagnosis which may produce a similar presentation to hyperparathyroidism is familial hypocalciuric hypercalcaemia, in which parathyroid hormone may not be suppressed, but in which urinary calcium is reduced, whereas this is raised in primary hyperparathyroidism.

Apart from its pro-arrhythmic effect the other main consequence of hypercalcaemia is impaired renal distal tubular action resulting in fluid loss and dehydration. Suggested management guidelines for hypercalcaemia are shown in *Figure 2*.

Hypocalcaemia

Hypocalcaemia can be defined as serum calcium adjusted for the serum albumin concentration below 2.15 mmol/litre, although ranges may differ slightly depending on method and population studies. Values under 1.9 mmol/litre merit immediate investigation, and those under 1.7 mmol/litre are liable to require increasingly urgent replacement, although rate of change is more important than absolute values (*Figure 3*).

The causes of hypoparathyroidism may be obvious (such as recent parathyroid or thyroid surgery) or require further investigation (autoimmune or more rarely amyloid or granulomatous parathyroid disease) (*Table 2*). Various inherited hypoparathyroid syndromes exist, including pseudohypoparathyroidism, which present first in adolescence or early adulthood. These may be suggested by a family history of calcium or endocrine disorders, although as the modes of inheritance vary a history may not be found.

Vitamin D deficiency may be suspected from the clinical context – malnutrition or limited sun exposure, particularly combined with dark skin colour, malabsorption or from other known gastrointestinal, liver or renal disease.

Hypomagnesaemia is a common finding particularly in elderly patients and should be considered as a possible cause of hypocalcaemia as it interferes with the secretion and action of parathyroid hormone. Hypomagnesaemia should be considered in particular in patients with malabsorption, those on diuretics and patients in whom the hypocalcaemia appears to be resistant to replacement.

Finally, a range of drugs may lower calcium either as intentional therapeutic use or by a range of different effects (*Table 2*). Suggested management guide-

Figure 2. Sample guidelines for urgent management of hypercalcaemia.

For moderate hypercalcaemia (3.0–3.5 mmol/litre)	
Request serum parathyroid hormone if cause unknown before starting rehydration	
Assess hydration status and rehydrate as required with saline, 4–6 litres over 24 hours monitoring fluid balance carefully. Catheterization may be required, particularly in patients with cardiac or renal dysfunction	
Avoid thiazide diuretics. If heart failure present, consider furosemide orally or intravenously as drug of choice	
Repeat serum calcium after 24 hours rehydration if initial calcium <3.5 mmol/litre to determine need for bisphosphonate therapy	
For severe hypercalcaemia (above 3.5 mmol/litre or rapidly rising with symptoms) or if hypercalcaemia at or >3.0 mmol/litre after rehydration when initially below 3.5 mmol/litre, give bisphosphonates intravenous as follows but reduce dose or infusion rate if renal impairment (see British National Formulary appendix 3.)	
Pamidronate (over 2 hours in 100–500 ml saline)	90 mg if adjusted Ca > 3.0 mmol/litre
	60 mg if adjusted Ca < 3.0 mmol/litre and calcium lowering still considered appropriate
Serum calcium response to pamidronate takes 48 hours. Intravenous pamidronate should not be repeated without senior medical review	
If adjusted calcium above 4.0 mmol/litre consider calcitonin 100 units 3 times per day subcutaneously for 24–48 hours if using pamidronate	
If no response in 5 days after adequate hydration and pamidronate consider zoledronic acid 4 mg in 50 ml saline over 15 minutes. Zoledronic acid may be considered first line in hypercalcaemia of malignancy	

Figure 3. Assessment of unexplained low serum adjusted calcium (ACa).

Repeat within 1 week to confirm unless patient acutely unwell, value falling rapidly or ACa under 1.9 mmol/litre	
Assess symptoms	Peripheral paraesthesiae
	Cramps
	Psychological changes
	Seizures
	Bronchospasm
	Tetany
	Dystonic movements, Chvostek or Trousseau signs
	Electrocardiogram: long QT interval or arrhythmia
	Cataract
Consider	Possible spurious result (mainly contamination from calcium EDTA blood collection tube (full blood count tube), but also citrate or oxalate contamination)
	Effect of high albumin concentration on calcium adjustment
Consider causes related to patient history	Renal or hepatic disease
	Parathyroid or thyroid surgery
	Drug history
	Predisposing factors for vitamin D deficiency: malnutrition, housebound or malabsorption
Check phosphate, alkaline phosphatase and creatinine results	
Assess urgency: ACa 1.75–2.15 mmol/litre	Oral replacement may be sufficient while cause is being established unless falling rapidly or patient symptomatic
ACa ≤ 1.75 mmol/litre	Immediate replacement likely to be necessary

Table 2. Causes of hypocalcaemia

Hypoparathyroidism (inherited and acquired) (22%)	Parathyroid or thyroid surgery
	Autoimmune hyperparathyroidism
	Hypomagnesaemia
	Inherited (pseudohypoparathyroidism and others)
Vitamin D deficiency (73%)	Malnutrition and malabsorptive diseases
	Low sun exposure or housebound
	Liver disease
	Renal disease
	Hyperphosphataemia
Drugs (3%)	Inhibiting bone resorption: bisphosphonates, calcitonin-cinacelet
	Cytotoxics: cisplatin, cytosine, doxorubicin
	Antimicrobials: ketoconazole
	Furosemide
	Anticonvulsants (phenytoin)
Extensive osteoblastic activity (2%)	Osteoblastic metastases, 'hungry bone syndrome'

lines for hypocalcaemia are shown in *Figure 4*.

Hyperphosphataemia

Hyperphosphataemia may arise either through increased phosphate input to blood or reduced removal. One of the commonest causes is artefactual as a result of sample haemolysis. Apart from iatrogenic causes (infused phosphate or phosphate enemas) increased input is mostly the result of cell death (e.g. tumour lysis, rhabdomyolysis). Reduced excretion occurs as a result of low glomerular filtration in advanced renal failure, or increased phosphate absorption, in vitamin D excess or hypoparathyroidism, both of which are fairly rare. An additional iatrogenic cause to consider, particularly with their increasing use, is the bisphosphonates. The main consequence of prolonged hyperphosphataemia is soft tissue calcification when the calcium/phosphate solubility product is exceeded. Oral phosphate binders (aluminium hydroxide, calcium acetate, lanthanum or sevelamer) are used in these situations. The cause is usually apparent, and apart from the hypocalcaemia produced by acute hyperphosphataemia (such as tumour lysis syndrome) it is usually asymptomatic. Suggested management guidelines for hyperphosphataemia are shown in *Figure 5*.

Hypophosphataemia

Hypophosphataemia in hospital practice is usually caused by a combination of low phosphate reserves as a result of illness or malnutrition combined with acute shift of phosphate from the small percentage in the extracellular compartment to the majority intracellular compartment as a result of refeeding, respiratory alkalosis or extensive muscle effort. Mild hypophosphataemia (above 0.35 mmol/litre) rarely has clinical consequences and does not usually require correction. Acute severe hypophosphataemia results in tissue hypoxia, muscle pain and weakness including respiratory difficulties, impaired leukocyte function predisposing to infection, and central effects ranging from lethargy to coma.

As refeeding syndrome in malnourished patients is a major iatrogenic cause, at-risk patients should be identified and given supplementary phosphate as part of their feeding or parenteral nutrition regimen. **BJHM**

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Conflict of interest: none.

Figure 4. Sample guidelines for urgent management of hypocalcaemia.

If acute symptomatic hypocalcaemia or serum adjusted calcium < 1.5 mmol/litre:

Give 10 ml 10% calcium gluconate (2.25 mmol/litre) by slow intravenous injection over 5–15 mins

Follow with 40 ml 10% calcium gluconate (9 mmol) daily in 500 ml normal saline over 6 hours

For less severe hypocalcaemia <1.7 mmol/litre the daily infusion can be used

Measure serum magnesium if serum adjusted calcium <1.75 mmol/litre

If Mg <0.4 mmol/litre give intravenous Mg sulphate to correct Mg and Ca

Monitor serum-adjusted Ca every 4 hours for first day, then daily

(Monitor Mg daily if low)

Figure 5. Sample guidelines for urgent management of hypophosphataemia.

If serum phosphate < 0.3 mmol/litre (or 0.4 mmol/litre in alcoholic patients) give intravenous replacement

If serum phosphate > 0.3 mmol/litre but <0.4 mmol/litre, recheck next day

Intravenous phosphate replacement:

Give 50 mmol phosphate over 8 hours as, for example, 500 ml phosphate Polyfusor

If serum potassium above 6 mmol/litre or patient fluid restricted give 50 mmol phosphate as sodium glycerophosphate diluted to 250 ml with 5% glucose over 6 hours (one 20ml vial of sodium glycerophosphate contains 20 mmol phosphate)

On day 2 give 20 mmol phosphate

Avoid in acute pancreatitis

Monitor calcium, phosphate and magnesium daily

KEY POINTS

- The causes of calcium and phosphate abnormalities is usually clinically apparent.
- Parathyroid hormone measurement distinguishes the main causes in unexplained cases of hypercalcaemia.
- Hyperparathyroidism and malignancy-associated hypercalcaemia (with suppressed parathyroid hormone) are the commonest causes of hypercalcaemia.
- Malabsorption, malnutrition and low sunlight exposure should be considered as causes of hypocalcaemia.
- Hypomagnesaemia is an additional often unrecognized important cause of hypocalcaemia.