RATIONAL TESTING

Investigating hypocalcaemia

This article explores how to confirm hypocalcaemia and ascertain its causes

Fadil M Hannan clinical lecturer1,2, Rajesh V Thakker May professor of medicine1

1Academic Endocrine Unit, Oxford Centre for Diabetes, Endocrinology and Metabolism, Nuffield Department of Clinical Medicine, University of Oxford, Churchill Hospital, Oxford OX3 7LJ, UK; 2Department of Clinical Biochemistry, John Radcliffe Hospital, Oxford OX3 9DU, UK

This series of occasional articles provides an update on the best use of key diagnostic tests in the initial investigation of common or important clinical presentations. The series advisers are Steve Atkin, professor, head of department of academic endocrinology, diabetes, and metabolism, Hull York Medical School; and Eric Kilpatrick, honorary professor, department of clinical biochemistry, Hull Royal Infirmary, Hull York Medical School. To suggest a topic for this series, please email us at practice@bmj.com.

A 42 year old woman with active Crohn’s disease presented to her general practitioner for annual review. Serum electrolyte, renal and liver function tests were normal apart from the following: total calcium 2.04 mmol/L (normal range 2.20–2.60 mmol/L); albumin 38 g/L (35–50 g/L); phosphate 0.71 mmol/L (0.80–1.45 mmol/L); and alkaline phosphatase activity 380 U/L (80–290 U/L). She had no history of paraesthesiae, carpopedal spasms, or seizures. Subsequent investigations showed a low serum 25-hydroxyvitamin D (25(OH)D) concentration of 23 nmol/L (normal >75 nmol/L). She was therefore started on oral calcium and cholecalciferol daily. Four months later, the patient presented to the local emergency department with persistent severe diarrhoea, paraesthesiae, carpal spasms, and seizures. Investigations found no causes for the seizures other than hypocalcaemia (ionised plasma calcium 0.82 mmol/L; normal range 1.1–1.30 mmol/L).

What are the next investigations?

• Confirm hypocalcaemia by measurement of serum albumin-adjusted calcium (albumin-adjusted calcium = total calcium + 0.016 x (40 – albumin)). At admission this patient’s serum calcium is 1.56 + 0.016 x (40 – 35) = 1.64 mmol/L.
• In critically ill patients or those with acid-base disorders and symptoms attributable to hypocalcaemia, measure ionised calcium on a blood sample obtained without a tourniquet.
• Define causes of hypocalcaemia by measuring serum parathyroid hormone concentrations.
• Assess serum magnesium.
• Other first line tests include serum phosphate and creatinine concentrations, and estimated glomerular filtration rate to help elucidate causes.

These tests are outlined in the figure⇑ and discussed in detail below.

The prevalence of hypocalcaemia has been reported as >15% and 85% in hospitalised and critically ill patients, respectively. The clinical presentation of hypocalcaemia (serum albumin-adjusted calcium <2.20 mmol/L or ionised calcium <1.1 mmol/L) ranges from an asymptomatic biochemical abnormality to a life threatening disorder. Patients with severe hypocalcaemia (serum albumin-adjusted calcium <1.90 mmol/L or ionised calcium <0.95 mmol/L) may develop symptoms of acute neuromuscular irritability. Paraesthesiae of the circumoral region, fingers, and toes occurs most commonly. However, patients may also develop muscle cramps, carpopedal spasms, seizures of all types, and cardiac arrhythmias associated with prolongation of the QT interval on electrocardiography. Chronic hypocalcaemia (over several years) may be associated with subcapsular cataracts; papilloedema; abnormal dentition; and ectopic calcification (such as in the basal ganglia).

Serum albumin-adjusted calcium and ionised calcium in diagnosing hypocalcaemia

The diagnosis of hypocalcaemia should be based on the measurement of serum albumin-adjusted calcium concentrations. Serum total calcium is adjusted to the prevailing serum albumin concentration, as about half of the circulating calcium is bound mainly to albumin, and also to globulins, bicarbonate, and other anions. Thus, alterations in albumin concentrations alone will lead to changes in total calcium without affecting the biologically important ionised calcium fraction. One of the most widely used methods of adjustment is to add or subtract 0.1 mmol/L from the total calcium concentration for every 6 g/L of albumin below or above a reference value of 40 g/L.
Learning points

- To confirm hypocalcaemia, calculate serum albumin-adjusted calcium concentrations; in patients who are critically ill or have acid-base disorders, ionised calcium measurements are needed.
- Careful clinical assessment may show common causes of hypocalcaemia, such as post-surgical hypoparathyroidism, chronic kidney disease, or drugs.
- Serum parathyroid hormone measurements are central to investigating and classifying causes of hypocalcaemia; other tests include serum phosphate, magnesium, and creatinine concentrations.
- Serum vitamin D measurements are indicated in patients with inadequate exposure to sunlight, nutritional deficiency, or malabsorption syndrome.

Serum parathyroid hormone measurement for defining cause of hypocalcaemia

Measurement of serum parathyroid hormone concentration, plus concurrent serum albumin-adjusted calcium, is central to investigating hypocalcaemia and is used to classify its causes (box). Circulating ionised calcium concentrations are tightly regulated by parathyroid hormone, which stimulates osteoclastic bone resorption, inhibits the renal excretion of calcium, and promotes the renal synthesis of 1,25-dihydroxyvitamin D (1,25(OH)_2D), leading to enhanced intestinal absorption of calcium. A low or normal serum parathyroid hormone concentration linked with hypocalcaemia is consistent with hypoparathyroidism (box), whereas a raised concentration indicates secondary hyperparathyroidism, which is commonly caused by disorders such as chronic kidney disease or vitamin D deficiency (box).

However, serum parathyroid hormone measurements may not be available on a same day basis, and appropriate clinical assessment and interpretation of more readily available serum measurements may help to uncover the cause of hypocalcaemia (figure). Thus, the first step in establishing the cause of hypocalcaemia is a careful history and examination focusing on the predisposing causes, such as chronic kidney disease, neck surgery, drugs, vitamin D deficiency, autoimmune disease, malabsorption syndrome, or dysmorphic features consistent with a congenital disorder (box, figure).

Serum creatinine concentrations and estimated glomerular filtration rate

These will help to confirm renal impairment (figure)—hypocalcaemia is typically observed in stage 5 of chronic kidney disease (estimated glomerular filtration rate <15 ml/min/1.73m^2). Hypocalcaemia in chronic kidney disease is secondary to the reduced synthesis of 1,25-dihydroxyvitamin D and the occurrence of hyperphosphataemia, which leads to an increase in the calcium phosphate product and precipitation of calcium phosphate in soft tissues, thereby lowering circulating calcium concentrations.

Serum phosphate concentrations

Measurement of serum phosphate may be helpful for diagnosing the cause of the hypocalcaemia, as hypoparathyroid disorders are associated with hyperphosphataemia, whereas low serum phosphate concentrations are associated with high parathyroid hormone concentrations as occur in secondary hyperparathyroid states such as vitamin D deficiency and osteomalacia (figure). However, serum phosphate varies greatly within an individual owing to the effects of circadian variation and dietary intake.

Serum magnesium concentrations

These are helpful as a first line investigation, as hypomagnesaemia is associated with an impairment of parathyroid hormone secretion and end-organ resistance to the effects of parathyroid hormone. Serum magnesium concentrations <0.5 mmol/L typically result in symptomatic hypocalcaemia. Hypomagnesaemia may occur in patients with acute or chronic diarrhoea, malabsorption syndromes, or alcoholism or in those taking proton pump inhibitors or loop or thiazide diuretics.

Serum 25-hydroxyvitamin D concentrations

Vitamin D deficiency (as assessed by serum concentration of 25-hydroxyvitamin D, its major circulating form) is a major cause of hypocalcaemia and commonly affects elderly people, people living in a care home, and individuals of non-white ethnicity. The deficiency occurs as a consequence of inadequate exposure to sunlight (for example, wearing skin concealing garments, or using excessive amounts of sunscreen); nutritional deficiency (such as in exclusively breastfed infants); and malabsorption syndrome (such as those with coeliac disease, Crohn’s disease, short bowel syndrome, cystic fibrosis, or chronic pancreatic insufficiency).

Vitamin D deficiency should be considered in a patient with clinical features of osteomalacia or rickets, hypophosphataemia, increased serum alkaline phosphatase activity or raised parathyroid hormone concentrations. Vitamin D deficiency is generally defined by a serum 25-hydroxyvitamin D concentration of <50 nmol/L, although hypocalcaemia is not usually observed until the concentration is as low as <25 mmol/L.

Serum amylase concentrations

These are helpful for the detection of acute pancreatitis (figure).
Serum creatine kinase concentrations

These are helpful for the detection of early rhabdomyolysis (figure⇓).

Outcome

Additional history from her relatives showed that she had not taken the prescribed oral calcium and cholecalciferol. Serum biochemical investigations undertaken at the time of admission showed the following abnormal concentrations: an albumin-adjusted calcium of 1.64 mmol/L, phosphate of 0.66 mmol/L, magnesium of 0.36 mmol/L (normal range 0.75-1.05 mmol/L), and parathyroid hormone of 10.8 pmol/L (normal range 1.3-7.6 pmol/L). This patient was diagnosed with hypocalcaemia associated with secondary hyperparathyroidism, hypomagnesaemia, and vitamin D deficiency resulting from malabsorption from extensive small bowel Crohn’s disease. She was treated with intravenous infusions of calcium gluconate and magnesium and oral high dose cholecalciferol, as well as glucocorticoids for active Crohn’s disease.

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16 Pearce SH, Cheetham TD. Diagnosis and management of vitamin D deficiency. BMJ 2010;340:c6564.

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Fig 1 Clinical approach to the investigation of common causes of hypocalcaemia

**Hypocalcaemia**
Serum adjusted calcium <2.2 mmol/L
or ionised calcium <1.1 mmol/L

**Clinical assessment** - for risk factors for vitamin D deficiency and for common causes of hypocalcaemia (eg, CKD, post-surgical hypoparathyroidism, or drugs)

**Other serum biochemical tests**
- Phosphate
- Magnesium
- Creatinine + eGFR
- PTH
- Amylase
- Creatine kinase
- 25-hydroxyvitamin D

First line

- Reduced phosphate + raised PTH
- Raised phosphate + reduced PTH
- Raised phosphate + raised PTH

**Vitamin D deficiency**
- Acute pancreatitis
- Drugs (eg, bisphosphonates)

**Hypomagnesaemia**
- Hypoparathyroidism
- Drugs (eg, cinacalcet)

**CKD**
- Massive tumour lysis
- Early rhabdomyolysis

CKD = chronic kidney disease
eGFR = estimated glomerular filtration rate
PTH = parathyroid hormone