Management of acute renal failure and hypercalcaemia

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The immediate management and investigation of an acute endocrine presentation in general practice is discussed in this section. It is inspired by, but not based on, a real patient situation.

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Jane, aged 71 years, presents to you, her GP, with a three-month history of nausea, abdominal discomfort and reduced oral intake. She has had no vomiting or diarrhoea. Her family have noticed poor attention and concentration over the past few days. She has had associated weight loss of 5 kg over the past six weeks. Jane's past medical history includes hypertension since the age of 65 years, treated with amlodipine, a minimal trauma fracture of the forearm one year previously and renal calculus five years previously. There is no significant family history.

On examination, Jane has a blood pressure of 120/70 mmHg, with a postural drop of 15 mmHg. Her heart rate is 85 beats per minute and in sinus rhythm. She has dry mucous membranes and reduced skin turgor. Findings of her cardiovascular and respiratory examinations are normal. An abdominal examination reveals generalised tenderness but no guarding or rigidity. There is no renal bruit and Jane has bilateral pitting oedema peripherally.

Initial investigations reveal acute renal failure with hypercalcaemia. The results of these investigations are shown in Table 1.

How does hypercalcaemia present?

Answer: The prevalence of hypercalcaemia has been reported to be from 1.07 to 3.09% among nonhospitalised patients and 0.17 to 2.92% among hospitalised patients.[1] Patients with hypercalcaemia are most often asymptomatic and the condition is discovered incidentally during serum biochemistry tests.[2]

The clinical manifestations of hypercalcaemia are listed in Box 1.[2,3] Symptoms range from minor, such as constipation, to life-threatening, such as coma, and generally become apparent when the serum calcium concentration increases above 3 mmol/L.[2] Factors affecting the development of symptoms include patient age, comorbidities, duration of hypercalcaemia and the rate of increase in serum calcium concentration.[3]

What are the causes of hypercalcaemia?

Answer: In the absence of renal failure, more than 90% of cases of hypercalcaemia are due to primary hyperparathyroidism (PHPT) or malignancy.[4] Rapid elevation in calcium levels often indicates malignancy, whereas PHPT is a more insidious process, although acute on chronic deterioration resulting in a symptomatic hypercalcaemic presentation can occur. The remaining causes of hypercalcaemia represent a long and varied list of conditions, some of which are shown in Box 2.[3-6]

PHPT is the leading cause of hypercalcaemia in the general population. Excess secretion of parathyroid hormone (PTH) will:

- reduce renal calcium excretion
- promote phosphate excretion

Table 1. Results of Jane's initial investigations

Test	Result (reference range)
Sodium (mmol/L)	140 (135 to 145)
Potassium (mmol/L)	5.4 (3.5 to 5.0)
Chloride (mmol/L)	99 (97 to 107)
Bicarbonate (mmol/L)	28 (24 to 34)
Urea (mmol/L)	13.6 (3.1 to 8.1)
Creatinine (μmol/L)	201 (64 to 104)
eGFR (mL/min/1.73m^2)	21
Serum calcium (corrected) (mmol/L)	3.11 (2.20 to 2.55)
Magnesium (mmol/L)	0.9 (0.67 to 1.05)
Phosphate (mmol/L)	0.76 (0.78 to 1.43)

Abbreviation: eGFR = estimated glomerular filtration rate.

1. Clinical manifestations of hypercalcaemia[2,3]

Gastrointestinal
- Nausea, vomiting
- Anorexia
- Constipation
- Abdominal pain
- Peptic ulcer disease
- Acute pancreatitis

Cardiovascular
- Hypertension
- Vascular calcification
- Shortened QT interval
- Arrhythmias

Renal
- Polyuria
- Polydipsia
- Nephrolithiasis
- Nephrocalcinosis
- Nephrogenic diabetes insipidus
- Distal renal tubular acidosis

Neurological
- Confusion
- Apathy
- Drowsiness
- Coma

Other
- Fatigue
- Muscle weakness
- Bone pain
- Osteoporosis/osteopenia

- increase calcium absorption from the gut (via increased calcitriol production)
- increase calcium and phosphate release from bone.

The net result of excess secretion of PTH is hypercalcaemia with typically low or low-normal serum phosphate levels, unless phosphate excretion is impaired by concurrent renal failure.[7] PHPT is most commonly sporadic, being due to either a solitary PTH-secreting adenoma (80 to 85% of cases) or glandular hyperplasia.[4,7,8] Less than 1% of cases are due to parathyroid malignancies. About 5 to 10% of cases of PHPT are associated with inherited syndromes (Box 2).[7] Such conditions should be considered in young (<30 years) patients and those with a family history of hypercalcaemia, PHPT or neuroendocrine tumours.[7]

Malignancy is the second most common cause of hypercalcaemia in community-dwelling patients and the most common cause in hospitalised patients.[1,9] Hypercalcaemia occurs in 20 to 30% of patients with malignancy, usually late in the course of the disease.[5,10] It occurs when the tumour releases one or more substances (e.g. osteolytic cytokines, PTH, PTH-related protein or 1,25-dihydroxyvitamin D [1,25-$(OH)_2$ vitamin D]) that affect calcium homeostasis. Almost any cancer can cause hypercalcaemia, although myeloma and tumours of the lung and breast are most commonly implicated.[9]

Other well-described causes of hypercalcaemia include granulomatous disease, thyrotoxicosis, lithium use, use of thiazide diuretics, vitamin A toxicity and milk alkali syndrome.[3,10] Other iatrogenic causes, that are relatively common include overzealous calcium and calcitriol replacement in patients with post-surgical hypoparathyroidism and use of teriparatide (recombinant PTH) for treatment of patients with osteoporosis. In some cases, the cause of hypercalcaemia may be multifactorial.

How should Jane be managed?

Answer: The management of patients with hypercalcaemia depends largely on the severity of hypercalcaemia and the presence of symptoms. Hypercalcaemia can be classified according to the serum calcium level as mild (2.5 to 3.0 mmol/L), moderate (3.0 to 3.5 mmol/L) or severe (>3.5 mmol/L).[2]

Patients with mild hypercalcaemia are usually asymptomatic and do not require urgent treatment. However, they are at risk of developing more severe hypercalcaemia and should be advised to avoid dehydration and precipitating medications, such as thiazides and lithium. Patients with acute moderate hypercalcaemia require immediate treatment if they are symptomatic and dehydrated, confused or drowsy. Those with severe hypercalcaemia commonly have symptoms and require referral for urgent treatment.

Jane undergoes an ECG, which does not reveal any abnormality. Given her symptoms, delirium, acute renal impairment and the severity of hypercalcaemia, she is referred to the emergency department for further management.

2. Causes of hypercalcaemia[3-6]

Primary hyperparathyroidism
- Sporadic
  - adenoma (85%)
  - parathyroid hyperplasia
  - parathyroid malignancy (<1%)
- Inherited syndromes (5 to 10%)
  - multiple endocrine neoplasia (MEN) type 1, 2A or 4
  - hyperparathyroidism jaw tumour syndrome
  - familial isolated hyperparathyroidism
  - familial hypocalciuric hypercalcaemia

Malignancy
- Humoral hypercalcaemia (80%) due to parathyroid hormone (PTH)-related peptide e.g. squamous cell carcinoma, renal, endometrial, ovarian or breast cancer
- Local osteolytic disease (20%) e.g. breast cancer, myeloma or lymphoma
- 1,25-dihydroxyvitamin D secretion (<1%) e.g. lymphoma
- Ectopic PTH production (<1%)

1,25-dihydroxyvitamin D-related
- Hypervitaminosis D
- Granulomatous disease
  - sarcoidosis
  - tuberculosis
  - inflammatory bowel disease
  - nonparathyroid endocrine disorders
- Thyrotoxicosis
- Adrenal insufficiency
- Phaeochromocytoma
- Vasoactive intestinal polypeptide (VIP)-producing tumour

Drug-related
- Lithium
- Thiazide diuretics
- Oestrogens and antioestrogens
- Vitamin A
- Vitamin D
- Teriparatide
- Theophylline toxicity

Other
- Calcium and calcitriol over-replacement
- Milk alkali syndrome
- Immobilisation
- Parenteral nutrition
- Chronic renal insufficiency
- Tertiary hyperparathyroidism
- Paget's disease
- Spurious hypercalcaemia from prolonged tourniquet time

What treatment does Jane require initially?

Answer: Treatment of patients with symptomatic or severe hypercalcaemia aims to correct fluid deficits, promote renal calcium excretion, inhibit bone breakdown (resorption) and, where possible, treat the underlying disease process.[3]

Adequate and appropriate hydration is required in patients with moderate chronic kidney disease (CKD), as optimising urine output is vital to ensure urinary calcium excretion. Intravenous fluids, such as isotonic saline, are the initial treatment for those with severe or acutely symptomatic hypercalcaemia. Expansion of the intravascular volume, which is often depleted, and increasing renal calcium excretion temporarily lowers, but rarely normalises, the serum calcium concentration. Typically, 4 to 6 L of fluid over 24 hours is required.[11]

Many patients, especially those with cardiovascular or renal disease, may not tolerate aggressive fluid administration and frusemide may be required to treat fluid overload. Frusemide further increases urinary calcium excretion, but the traditional method of lowering calcium via aggressive intravenous fluid therapy and forced diuresis is now rarely used due to the availability of more effective calcium-lowering agents, most commonly intravenous bisphosphonates. Unless the underlying causative process is corrected, calcium concentrations generally return to pretreatment levels after cessation of intravenous fluids.

Bisphosphonates, such as disodium pamidronate and zoledronic acid, prevent the release of calcium from bone stores into the circulation by inhibiting bone resorption. These drugs lower the serum calcium concentration within 24 to 72 hours of administration and have a duration of action of two to four weeks.[12] They are effective in several conditions including hypercalcaemia due to malignancy and hyperparathyroidism, and can be used empirically in patients with severe or symptomatic hypercalcaemia.[11,12] Typically, disodium pamidronate 60 to 90 mg or zoledronic acid 4 mg is used. Because of the risk of nephrotoxicity, optimal hydration is essential and dose reduction may be warranted in the setting of renal impairment, as in Jane's case. The newer antiresorptive agent, denosumab, has also been used in the management of patients with severe hypercalcaemia, particularly in the setting of malignancy that is refractory to bisphosphonates. Denosumab may be preferable if the patient has significant coexisting CKD.

In severe or life-threatening situations where serum calcium levels must be lowered rapidly, calcitonin can be administered in conjunction with intravenous fluids, corticosteroids and a bisphosphonate. Calcitonin both inhibits bone resorption and promotes renal calcium excretion.[3] It acts within four to six hours of administration, but its effects diminish after 48 hours, even with continued administration, because of the development of tachyphylaxis.[12] Haemodialysis may rarely be required in emergency situations or in patients with severe CKD.

Careful monitoring of serum calcium levels is important to avoid overtreatment and the development of hypocalcaemia.

Jane is rehydrated with 2 L of normal saline and given 30 mg of an intravenous bisphosphonate, disodium pamidronate, with careful monitoring of her fluid status and renal function over subsequent days.

What further investigations should be performed?

Answer: Once the patient's serum calcium level has been reduced, efforts should be focused, where possible, on identifying and treating the underlying cause of the hypercalcaemia. This may involve reviewing offending medications (e.g. thiazides), surgically removing a parathyroid adenoma, giving chemotherapy for malignancy or treating granulomatous disease with corticosteroids. Beyond their anti-inflammatory properties, corticosteroids inhibit the enzyme 1-alpha-hydroxylase, which is overproduced in granulomatous tissue and results in excess synthesis of the active hormone 1,25-$(OH)_2$ vitamin D, which promotes calcium and phosphate absorption. In settings where the aetiology of hypercalcaemia is uncertain, a clear response to a trial of corticosteroids (i.e. 25 to 50 mg prednisone) can be a clue to the diagnosis.

A pathway for the investigation of patients with hypercalcaemia such as Jane is shown in the Flowchart.

Results of Jane's further investigations (Table 2) confirm an inappropriately elevated PTH level in the setting of persistently elevated calcium levels. A renal ultrasound reveals normal-sized kidneys, no urinary tract obstruction and no renal calculi.

How should the investigation results be interpreted?

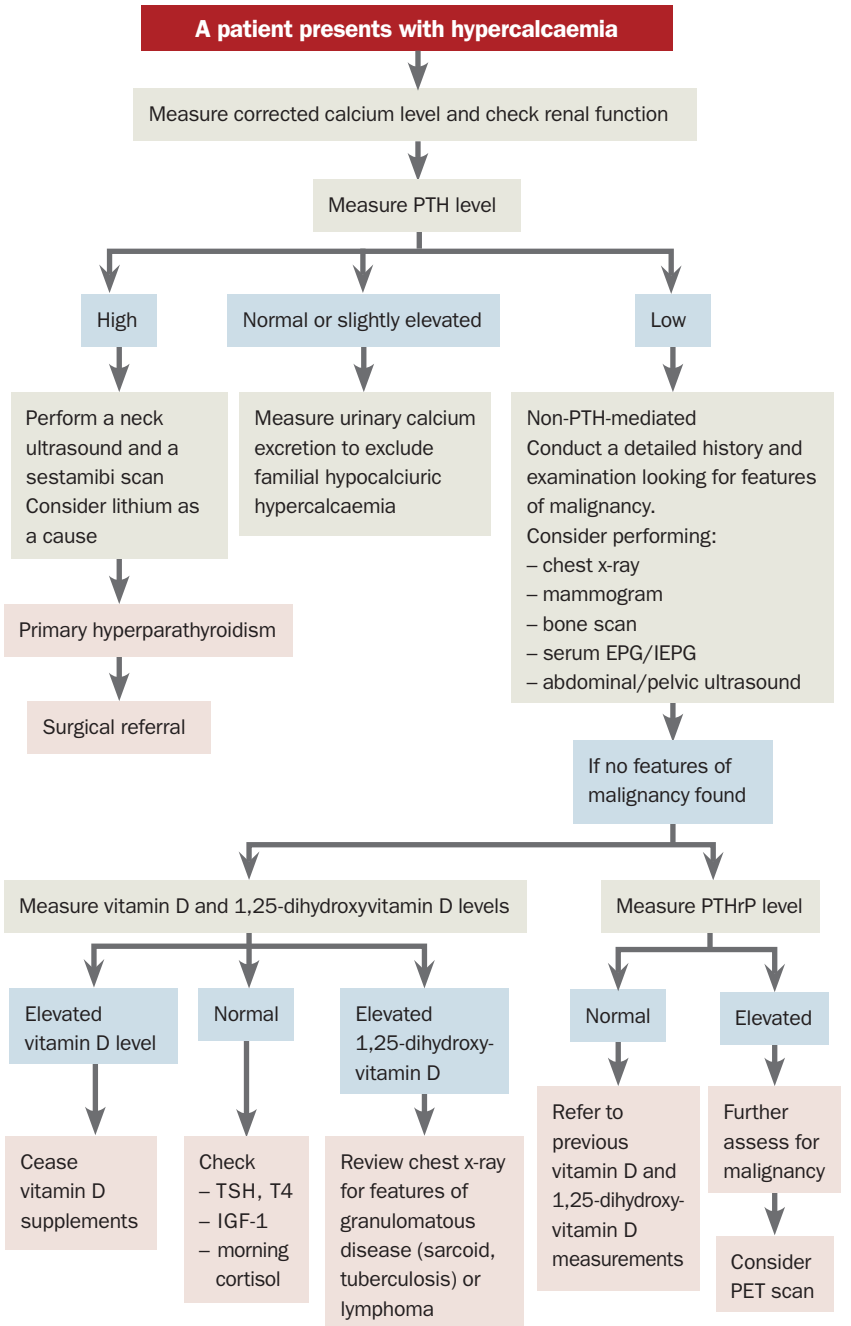
Answer: Elevated calcium levels should be reconfirmed, to exclude spurious hypercalcaemia, for example from excessive length of tourniquet application. In the context of elevated calcium levels, it is expected that the PTH level will be low. The presence of a detectable or elevated PTH level confirms autonomous PTH secretion from PHPT.

In the setting of mild asymptomatic hypercalcaemia, familial hypocalciuric hypercalcaemia (FHH) should be considered before the diagnosis of PHPT can be made.[13] FHH is a genetic condition that alters the 'setpoint' for serum calcium levels, resulting in life-long elevation of calcium levels without significant clinical consequence. Urinary excretion of calcium is low in those with FHH, rather than the elevated levels seen in patients with PHPT. In those with a normal vitamin D concentration, a calcium:creatinine clearance ratio less than 0.01 is suggestive of FHH. This can be calculated on a spot morning urine sample, or a 24-hour collection, using the following equation:

(urine calcium in mmol per L x [serum creatinine in µmol per L/1000]) / (serum calcium in mmol per L x urine creatinine in mmol per L).

When a patient's PTH concentration is low, PTH-independent causes of hypercalcaemia, should be considered, including malignancy, granulomatous disease, hypervitaminosis D or other endocrinopathy. Investigations for malignancy should be guided by the patient's history and examination findings. In the absence of an overt malignancy, investigations to consider include chest x-ray, mammography, serum immunoelectrophoresis, free light chain assay, abdominal and pelvic ultrasounds and bone scan.[8] Secretion of PTH-related peptide (PTHrP)

An approach to investigation of patients with hypercalcaemia



Abbreviations: EPG = electrophoresis; IEPG = immunoelectrophoresis; IGF-1 = insulin-like growth factor-1; PET = positron emission tomography; PTH = parathyroid hormone; PTHrP = parathyroid hormone-related protein; T4 = thyroxine; TSH = thyroid-stimulating hormone.

by tumour cells is the underlying mechanism in 80% of cases of malignant hypercalcaemia.[5] PTHrP can be measured if the diagnosis remains unclear, but the assay is performed infrequently in Australia. Endocrine investigations, including thyroid function tests and measurement of morning cortisol levels, should be performed as clinically indicated.

Based on the elevated PTH level, Jane is diagnosed with PHPT. There is no other cause for Jane's renal failure, with no urinary tract infection, negative autoimmune and vasculitic screen, and negative myeloma screen. The normal 1,25-$(OH)_2$ vitamin D and ACE levels are consistent with the diagnosis of PHPT.

What are the indications for surgical intervention in patients with PHPT?

Answer: Once a biochemical diagnosis of PHPT has been established, the next step is to determine whether surgical management is warranted. The indications for surgical intervention for PHPT are listed in Box 3.[14]

If surgery is indicated then imaging studies can help to facilitate surgical planning. The role of parathyroid imaging is primarily to identify an unequivocal single adenoma that may be amenable to a focussed minimally invasive surgical approach. Imaging studies should not be used to diagnose hyperparathyroidism, because there is a high false-positive rate, ranging from 5 to 25%.[15]

The traditional surgical approach to PHPT is a four-gland exploration, as pathologies may include single adenoma, double adenoma, diffuse or nodular hyperplasia, or carcinoma; these are not always distinguishable on imaging alone. Combining a neck ultrasound and technetium-99m sestamibi scan, performed in a specialist centre, can clearly locate a causative lesion in up to 95% of cases.[8,16] A four-dimensional CT scan looking at the arterial and venous phases after injection of contrast can assist in localisation of the lesion if a sestamibi scan and ultrasound have not been successful in localisation of the lesion. Four-gland exploration is recommended if imaging studies are negative, or surgical findings do not confirm a single parathyroid adenoma. This is more likely associated with genetic syndromes causing familial hyperparathyroidism.

Patients who do not meet the criteria for surgical management can be managed conservatively, with regular monitoring of calcium levels, bone density and renal parameters. Patients who decline surgery or are considered an unacceptable surgical risk may achieve control of calcium levels with regular use of bisphosphonates, denosumab or cinacalcet (a drug that reduces the setpoint of the

Table 2. Results of Jane's further investigations

Test	Result (reference range)
Serum calcium (corrected) (mmol/L)	2.86 (2.20 to 2.55)
Parathyroid hormone (ng/L)	95 (<50)
25-hydroxyvitamin D (nmol/L)	36.8 (50 to 130)
1,25-dihydroxyvitamin D (pmol/L)	83 (38 to 160)
24-hour urinary calcium (mmol/24 h)	10.46 (1.25 to 7.5)
Serum and urine electrophoresis	No paraprotein; mild proteinuria, polyclonal free light chain
Midstream urine culture	No growth, no cells seen
Antinuclear antibody	Negative
Antineutrophil cytoplasm antibody	Negative
Extractable nuclear antigen	Negative
Angiotensin-converting enzyme level (U/L)	48 (40 to 135)

3. Indications for surgical intervention in patients with primary hyperparathyroidism[14]

- Serum calcium levels 0.25 mmol/L or more above the upper limit of reference range
- Renal failure with estimated glomerular filtration rate <60 mL/min/1.73m^2
- Osteoporosis with T score <–2.5 at femoral neck, lumbar spine or distal radius
- 24-hour urinary calcium excretion >10 mmol/24 h
- Nephrolithiasis or nephrocalcinosis on imaging
- Acute pancreatitis and refractory peptic ulcer
- Younger than 50 years of age

PTH–calcium curve but does not increase bone mineral density; not available on the PBS). Percutaneous ethanol injection of a clearly localised adenoma may be an option in selected patients.

Jane undergoes dual-energy x-ray absorptiometry/bone mineral densitometry which shows T-scores in the osteoporotic range, consistent with her history of minimal trauma fracture. Given her general good health, history of nephrolithiasis and the severity of hypercalcaemia and renal impairment, Jane is considered an appropriate candidate for surgical treatment, despite her age.

In the absence of a family history, the most likely cause of hypercalcaemia at Jane's age is a solitary parathyroid adenoma. If the adenoma is identifiable, Jane will be a candidate for minimally invasive surgery.

A technetium-99m sestamibi scan is performed, which shows increased uptake in the left inferior parathyroid gland. An ultrasound confirms the presence of a left inferior adenoma, with the remaining three glands being of normal size.

Jane is referred to a surgeon for a minimally invasive parathyroidectomy.

When should patients be referred for review?
Answer: Common situations where referral is required include the following.

- Patients with severe biochemical (>3.5 mmol/L) or acutely symptomatic hypercalcaemia should be referred to the emergency department for urgent management
- Patients with PHPT should be referred to an endocrinologist and endocrine surgeon for confirmation of diagnosis and assessment for surgical treatment
- Patients with hypercalcaemia that is related to a confirmed malignant process, should be referred to an appropriate cancer specialist
- When the aetiology of hypercalcaemia remains unclear, referral to an endocrinologist is appropriate.

Outcome: Postoperatively Jane's calcium levels and renal function return to normal. Her bone mineral density at one-year follow up has improved by 4% at the spine and 3% at the femoral neck, with no further falls or fractures.

Summary

Hypercalcaemia can manifest as gastrointestinal complaints (e.g. nausea, vomiting, constipation or abdominal pain), polyuria, polydipsia, bone pain, fatigue or altered mental state. The main causes of hypercalcaemia are PHPT and malignancy. Collectively, these causes account for more than 90% of cases in the setting of normal renal function.

Initial investigations for patients with hypercalcaemia include measurement of corrected serum calcium, phosphate, electrolytes, urea, and creatinine, PTH and vitamin D levels, and 24-hour urine calcium excretion.

Patients with acute symptoms or severe hypercalcaemia require treatment with intravenous fluids, followed by more definitive treatment based on the underlying aetiology. Patients with PHPT should be referred to an endocrinologist to confirm the diagnosis, and an endocrine surgeon for definitive surgical management. Temporising medical therapy with bisphosphonates may be required before surgery in patients with acute severe hypercalcaemia, or in those who are not surgical candidates. **ET**

References

A list of references is included in the website version of this article (www.endocrinologytoday.com.au).

COMPETING INTERESTS: None.

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