on regional fat distribution, insulin sensitivity, and cardiovascular risk factors in hypopituitary adults. *J Clin Endocrinol Metab* 1995;**80**:153–9.
12 Bulow B, Hagmar L, Mikoczy Z, Nordstrom CH, Erfurth EM. Increased cerebrovascular mortality in patients with hypopituitarism. *Clin Endocrinol (Oxf)* 1997;**46**:75–81.
13 Fowelin J, Attrall S, Lager I, Bengtsson BA. Effects of treatment with recombinant human growth hormone on insulin sensitivity and glucose metabolism in adults with growth hormone deficiency. *Metabolism* 1993;**42**:1443–7.
14 Rosen T, Bengtsson BA, Bennmarker H, Feldt-Rasmussen U *et al*. The influence of GH deficiency, GH replacement therapy and other aspects of hypopituitarism on fracture rate and bone mineral density. *J Bone Miner Res* 2001;**16**:398–405.
15 Drake WM, Howell SJ, Monson JP, Shalet SM. Optimising GH therapy in adults and children. Review. KIMS Study Group and the KIMS International Board. Pharmacia and Upjohn International Metabolic Database. *Endocr Rev* 2001;**22**:425–50.
16 Monson JP, Abs R, Bengtsson BA, Bennmarker H, *et al*. Growth hormone deficiency and replacement in elderly hypopituitary adults. *Clin Endocrinol (Oxf)* 2000;**53**:281–9.
17 Hernberg-Stahl E, Luger A, Abs R, Bengtsson BA *et al*. Healthcare consumption decreases in parallel with improvements in quality of life during GH replacement in hypopituitary adults with GH deficiency. *J Clin Endocrinol Metab* 2001;**86**:5277–81.

Hypercalcaemia

Peter Selby MA MD FRCP, Consultant Physician, Manchester Royal Infirmary; Honorary Senior Lecturer, University of Manchester, Department of Medicine, Manchester Royal Infirmary

Clin Med 2003;**3**:19–22

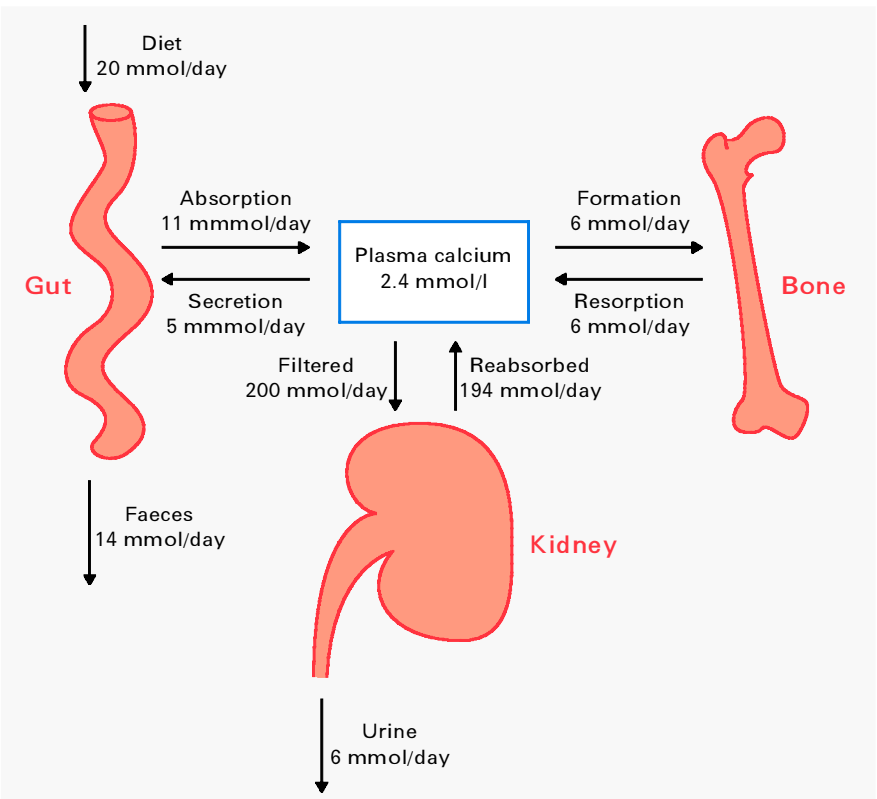
Hypercalcaemia is one of the more common metabolic abnormalities seen in hospital practice; it occurs in approximately 5% of hospital inpatients.[1] Hypercalcaemia results from an imbalance between the amount of calcium entering the plasma from the gastrointestinal tract or as a result of bone resorption and the amount being lost from the circulation through the urine or into newly formed bone. The overall fluxes in each of these systems are of a similar magnitude (Fig 1), but the net loss of calcium in the urine is the result of most of the filtered calcium being reabsorbed within the tubules. The level of calcium in the blood is therefore exquisitely sensitive to changes in both renal function and tubular handling of calcium.[2]

In most cases of hypercalcaemia a new steady state is reached in which calcium entering the circulation is balanced by that leaving it; this results in a stable situation in which the plasma calcium remains at a relatively constant level. However, when the hypercalcaemia is sufficient to impair renal function, either directly or as a result of dehydration, calcium excretion is impaired and the plasma calcium level increases. This results in further worsening of renal function, with consequent elevation of plasma calcium. This vicious circle is termed 'disequilibrium hypercalcaemia' and can rapidly lead to circulatory collapse if not treated with the appropriate degree of urgency.

Causes of hypercalcaemia

Most cases of hypercalcaemia in clinical practice will be the result of either primary hyperparathyroidism or malig-

Fig 1. Diagram indicating normal daily calcium fluxes in an adult.



nant disease. Less frequently, vitamin D intoxication or familial hypocalciuric hypercalcaemia are encountered as causes of raised calcium levels. Most of the other recognised causes of hypercalcaemia are rarely seen in clinical practice (Table 1).

Table 1. Causes of hypercalcaemia.

Common	Parathyroid dependent	Primary hyperparathyroidism Tertiary hyperparathyroidism
	Malignancy	Humoral hypercalcaemia Direct bone involvement: • multiple myeloma • bone metastases
Less common	Vitamin D intoxication	
	Familial hypocalciuric hypercalcaemia (abnormal sensing of calcium level)	
	Sarcoidosis and other granulomatous diseases (increased activation of vitamin D)	
Uncommon	Thiazide diuretics	
	Lithium therapy	
	Immobilisation (particularly where there is increased bone turnover, eg Paget's disease)	
	Hyperparathyroidism	
	Milk-alkali syndrome	
	Renal failure	
	Addison's disease	
	Vitamin A intoxication	

Diagnosis

Clinical examination

The clinical features of hypercalcaemia are usually of little diagnostic value as they are rarely sufficiently specific to allow differentiation from other conditions. Nevertheless, clinical history and examination are an important part of the assessment of any patient with hypercalcaemia. In addition to seeking the classical symptoms of the metabolic disorder (polyuria, polydipsia, vomiting, constipation and abdominal pain), it is also important to ascertain whether there is any evidence of end-organ damage. This might be suspected from a history suggesting renal stones or acute pancreatitis. Bone involvement by either hyperparathyroidism or malignant disease is suggested by the presence of skeletal pain. If it is possible to determine that the hypercalcaemia is long-standing, this is an important pointer in favour of hyperparathyroidism or other benign conditions. A drug history will help exclude vitamin D intoxication. Although thiazide diuretics are frequently cited as a cause of hypercalcaemia, it is more usual that they bring mild pre-existing hypercalcaemia to light.

Physical examination

Physical examination is usually unrewarding in establishing the diagnosis of hypercalcaemia but may give some clues towards any underlying malignant process. In patients with marked hypercalcaemia (plasma calcium >3 mmol/l), it is important to make an assessment of the state of hydration. Any suggestion of salt and water depletion might indicate the presence of disequilibrium hypercalcaemia and the need for urgent rehydration to prevent rapid deterioration.

Investigation

The diagnosis of hypercalcaemia itself is usually straightforward. Although emphasis has been placed upon the importance of measuring plasma calcium in the fasting state without venous stasis, neither of these precautions exerts a major influence on the level of measured plasma calcium. However, as calcium in the blood is approximately 50% bound to plasma proteins, it is important to correct the measured value for any abnormality of the protein level.[3]

Parathyroid hormone level

The most important investigation for elucidating the cause of hypercalcaemia is measurement of plasma parathyroid hormone (PTH) level. Unlike plasma calcium levels, this is influenced by food and should therefore be measured after an overnight fast. It is also important to take blood for the measurement of PTH before any attempt has been made to treat the plasma calcium because a fall in calcium can trigger PTH release, leading to the erroneous conclusion that the hypercalcaemia is PTH-dependent.

PTH concentrations in the upper part of the normal range in the presence of hypercalcaemia are usually indicative of parathyroid-dependent hypercalcaemia (primary or tertiary hyperparathyroidism). An important exception to this is familial hypocalciuric hypercalcaemia (FHH) which results from an inactivating mutation of the calcium sensing receptor. This causes the body to behave as if the calcium level is lower than it actually is. As a result, there may be elevated or high-normal PTH concentrations despite hypercalcaemia. FHH does not respond to parathyroidectomy, so this is an important differential diagnosis to exclude when such surgery is being considered.

Clearance ratio of calcium to creatinine

The generally accepted method of diagnosing FHH is to measure the clearance ratio of calcium to creatinine. This involves measuring calcium and creatinine in both plasma and urine following an overnight fast. The clearance ratio is calculated as follows:

$$\frac{Calcium\ (urine) \times creatinine\ (plasma)}{Creatinine\ (urine) \times calcium\ (plasma)}$$

In hypocalciuric hypercalcaemia the ratio is lower than 0.01, and in primary hyperparathyroidism generally higher than 0.02.

Vitamin D metabolites

In rare cases of vitamin D activation such as sarcoidosis, it may be useful to measure the level of vitamin D metabolites.

In other cases of hypercalcaemia it is generally sufficient to perform the standard investigations for the suspected underlying disease.

Renal tract

Assessment of the impact of chronic hypercalcaemia on the body involves examining the renal tract and skeleton. The presence of renal stones is most readily sought using ultrasonography. Some indication of kidney damage is given by 24-hour urine calcium excretion; values above 10 mmol/day are associated with a substantial risk of such complications.

The skeleton

Overt hyperparathyroid bone disease is rare, but mild hyperparathyroidism is not infrequently associated with osteoporosis. Bone density measurements should be part of the assessment of hyperparathyroid patients.

Parathyroid glands

Scanning of the parathyroid glands may be ordered as a precursor to surgery. This can be undertaken using computed tomography, ultrasonography or scintigraphy using technetium-labelled sestamibi. None of the available techniques has sufficient sensitivity or specificity to allow it to be used as a means of diagnosing hyperparathyroidism.

Management

With plasma calcium concentrations below 3 mmol/l the risk of significant symptoms of hypercalcaemia is low. The higher the calcium rises above this level the more likely it is both that symptoms will be present and that there may be acute metabolic consequences which need urgent treatment.

Severe symptomatic hypercalcaemia

In many instances severe symptomatic hypercalcaemia will need to be treated before a definitive underlying diagnosis is established. The most important aspect of management is vigorous rehydration, using saline to restore the extracellular volume and to obviate the risk of disequilibrium hypercalcaemia. Some authors suggest using frusemide to increase renal clearance of calcium. There is no evidence for its long-term effectiveness and, since diuretics worsen the risk of dehydration, frusemide is best reserved for those patients who retain fluid during rehydration.

Intravenous bisphosphonates should be given when the patient has been rehydrated. They are generally well tolerated, but a minority of patients may develop increased bone pain or a transient pyrexia and flu-like symptoms. Rarer complications include rashes and iritis.

Most patients will respond to intravenous bisphosphonates. For those who do not, treatment with calcitonin may be helpful. It may need to be given in high doses (up to 400 IU) by six-hourly intramuscular injection. It is often poorly tolerated, with side effects such as flushing and nausea. Some cases of resistant hypercalcaemia will respond to corticosteroid therapy; this needs to be given in high doses (eg prednisolone 40 mg/day).

Stable asymptomatic hypercalcaemia

With stable asymptomatic hypercalcaemia there is sufficient time to establish the diagnosis of the cause before starting treatment. The cause will usually be primary hyperparathyroidism.

Parathyroidectomy

There is still disagreement as to the place of parathyroidectomy. Some argue that in the absence of surgical contraindications the majority of patients should be offered surgery, whilst others reserve

Key Points

- The kidney is the most important organ for plasma calcium regulation
- Primary hyperparathyroidism and malignancy are the most common causes of hypercalcaemia
- Primary hyperparathyroidism is diagnosed on biochemistry, not by imaging
- Dehydration in a hypercalcaemic patient is potentially life-threatening
- Severe hypercalcaemia is initially treated by rehydration; bisphosphonates can be used when volume replete
- Not all patients with primary hyperparathyroidism require parathyroidectomy

KEY WORDS: bisphosphonates, calcium regulation, humoral hypercalcaemia of malignancy, hypercalcaemia, parathyroidectomy, primary hyperparathyroidism

Table 2. Indications for surgery in primary hyperparathyroidism.[4]

Definite	High serum calcium
	Previous disequilibrium hypercalcaemia
	Impaired renal function
	Renal stones
	Nephrocalcinosis
	High urinary calcium excretion (>10 mmol/24h)
	Reduced bone mineral density
Relative	Concomitant illness
	Difficulty of follow-up
	Younger patients (<50 years)
	Peptic ulcer disease
	Psychiatric complications
	Patient preference

operation for those with symptoms or in whom there is evidence of tissue damage by the hypercalcaemia. This situation is unlikely to change until a prospective study of parathyroidectomy is undertaken. Previous attempts to do this have all failed. The most widely accepted indications for parathyroidectomy were established by a National Institutes of Health consensus development conference in 1990, and modified in 2002.[5] These are summarised in Table 2. However, these recommendations are not evidenced based and have been criticised for this. In the UK, the Bone and Tooth Society has recently developed evidenced-based guidelines for the management of hyperparathyroidism.[6] These are less likely to lead to surgical intervention in any specific patient, but the overall indications for surgery are broadly similar (see Table 2).

Parathyroidectomy leads to normalisation of plasma calcium in most patients and is also associated with an increase in bone density.[7] However, the effect of surgery on the other complications of hyperparathyroidism is less clear-cut. Minimally invasive surgical procedures may make operative treatment more acceptable in the future.[8]

Medical therapy

In patients with mild disease or those with strong contraindications to surgery it is possible to consider medical therapy of hyperparathyroidism. Hormone replacement therapy is associated with a modest reduction in plasma and urine calcium together with preservation of bone density.[9] Although bisphosphonates are associated with preservation of bone mass, they do not appear to have a significant effect upon the plasma calcium level in the long term.[10]

References

1 Burt ME, Brennan MF. Incidence of hypercalcemia and malignant neoplasm. *Arch Surg* 1980;**115**:704–7.

2 Selby PL. Normal calcium homeostasis. *Clin Rev Bone Miner Metab* 2002;**1**:3–9.

3 Portale AA. Blood calcium, phosphorus and magnesium. In: Favus MJ (ed). *Primer on the metabolic bone diseases and disorders*, 1st edn. Kelseyville, CA: American Society for Bone and Mineral Research, 1990:62–4.

4 NIH Conference. Diagnosis and management of asymptomatic primary hyperparathyroidism: consensus development conference statement. Review. *Ann Intern Med* 1991;**114**:593–7.

5 Bilezikian JP, Potts JT Jr, El-Hajj Fuleihan G, Kleerekoper M, *et al*. Summary statement from a workshop on asymptomatic hyperparathyroidism. *J Bone Miner Res* 2002; **17**(Suppl 2):N2–N11.

6 Davies M, Fraser WD, Hosking DJ. Management of primary hyperparathyroidism. *Clin Endocrinol* 2002;**57**: 145–55.

7 Silverberg SJ, Shane E, Jacobs TP, Siris E, Bilezikian JP. A 10-year prospective study of primary with or without parathyroid surgery. *N Engl J Med* 1999;**341**:1249–55.

8 Miccoli P, Berti P. Minimally invasive parathyroid surgery. *Best Pract Res Clin Endocrinol Metab* 2001;**15**:139–47.

9 Orr-Walker BJ, Evans MC, Clearwater JM, Horne A *et al*. Effects of hormone replacement therapy on bone mineral density in postmenopausal women with primary hyperparathyroidism: four-year follow-up and comparison with healthy postmenopausal women. *Arch Intern Med* 2000; **160**:2161–6.

10 Rossini M, Gatti D, Isaia G, Sartori L *et al*. Effects of oral alendronate in elderly patients with osteoporosis and mild primary hyperparathyroidism. *J Bone Miner Res* 2001;**16**:113–9.