Clinical Reviews

A guide to the initial management of hypercalcaemia

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Abstract

With the widespread use of multiple channel biochemical auto analysers hypercalcaemia has become a common incidental finding. The approach to managing a patient with hypercalcaemia requires an understanding of the principles of calcium homeostasis, knowledge of the potential differential diagnoses and the clinical judgement to know when therapy is appropriate.

This article aims to provide a guide to the initial investigation and management of patients presenting with hypercalcaemia.

Keywords

Hypercalcaemia, calcium, malignancy, hyperparathyroidism

Key Points

- Hypercalcaemia may be asymptomatic or may present with a variety of non-specific symptoms.
- Hyperparathyroidism and malignancy are the commonest causes of hypercalcaemia.
- Intravenous rehydration, bisphosphonates and corticosteroids are the mainstay of treatment for malignant hypercalcaemia.

Introduction - Calcium homeostasis

Hypercalcaemia is a relatively common clinical finding with prevalence rates of 1.4-3.0% of hospitalised and general clinic populations.[1] In hospital, approximately 50% of patients with hypercalcaemia have malignancy and 17% have hyperparathyroidism whereas in the community hyperparathyroidism is the commonest cause.[2]

In the normal state hypercalcaemia is prevented by the suppression of parathyroid hormone secretion. This results in reduced bone resorption and a reduction in the renal production of $1,25(OH)_2$ Vitamin D leading to a reduction in calcium absorption from the intestine. More importantly, the reduction of parathyroid hormone (PTH) allows a marked increase in renal calcium excretion which is the principal route of calcium elimination, thereby resulting in marked hypercalciuria.

Mechanisms for the development of hypercalcaemia

The principal pathophysiologic alteration in severe hypercalcaemia is enhanced osteoclastic bone reabsorption. More rarely a reduction in the renal excretion of calcium may result in hypercalcaemia. Uniquely in the milk alkali syndrome hypercalcaemia occurs secondary to increased gastrointestinal absorption. Once hypercalcaemia is established, glomerular filtration and urinary concentrating ability may be impaired which predisposes to dehydration, vomiting and a further reduction in calcium clearance (see figure 1).

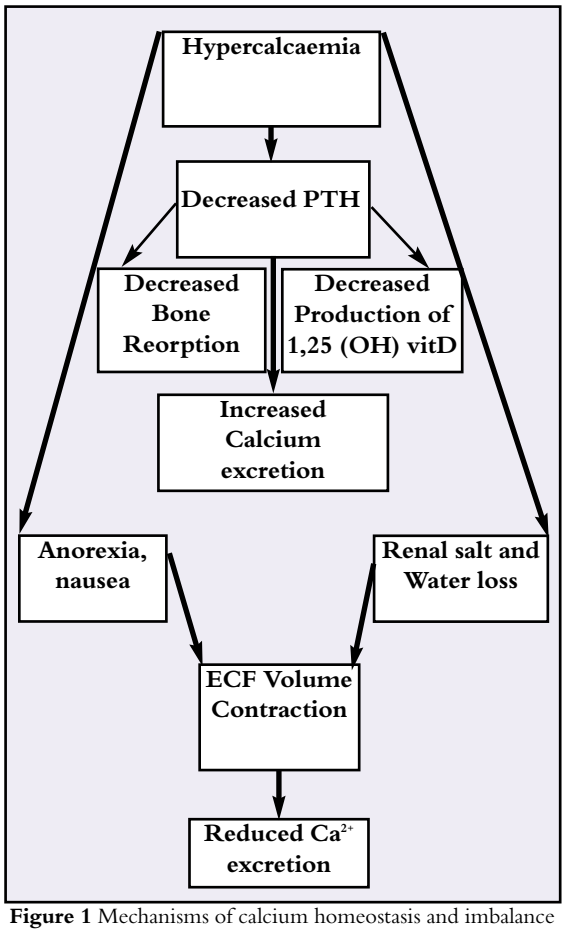

Figure 1 Mechanisms of calcium homeostasis and imbalance

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Presentation

Up to 85% of patients with hypercalcaemia are asymptomatic but neurological, gastrointestinal, renal, and cardiovascular disturbances may occur. The constellation of symptoms and signs associated with hypercalcaemia is often remembered from the saying 'stones, bones, groans and psychic moans' (See figure 2).

In hospital the commonest cause is malignancy, where the symptoms of hypercalcaemia such as fatigue and nausea may be mistakenly attributed to the underlying diagnosis. A high index of suspicion for hypercalcaemia is required in such patients.

Causes of Hypercalcaemia

Hyperparathyroidism and malignancy account for more than 90% of cases of hypercalcaemia.[3] Other causes of hypercalcaemia are listed in Table 1

Primary hyperparathyroidism

Primary hyperparathyroidism is the commonest cause of asymptomatic hypercalcaemia. The incidence is estimated as 42 per 100,000. It is affects twice as many females than males with a prevalence of up to 4/1000 women over 60. Primary hyperparathyroidism is commonest between the fourth and sixth decades of life. The diagnosis of primary hyperparathyroidism is confirmed by finding an elevated or inappropriately high normal parathyroid hormone level in conjunction with an elevated serum calcium level.

In the majority of cases, primary hyperparathyroidism results from a single adenoma of one of the four parathyroid glands, although hyperplasia, multiple adenomata and rarely carcinoma can be the cause. Primary hyperparathyroidism can sometimes occur as part of the syndromes of Multiple Endocrine Neoplasia (MEN) types 1 and 2A, and in isolated familial hyperparathyroidism

Very few patients now present with the classical features of hyperparathyroid bone disease or hyperparathyroid renal disease. Osteitis fibrosa cystica (subperiosteal erosions) is the characteristic feature of primary hyperparathyroidism. The commonest form of hyperparathyroid bone disease is osteoporosis. Renal calculi occur in fewer than 15% of patients with hyperparathyroidism and radiologically evident nephrocalcinosis is rare. However, unexplained deterioration in renal function is not uncommon.[15]

Hypercalcaemia of Malignancy

Malignant disease is a common cause of hypercalcaemia in hospitalised patients, occurring in up to 20% of patients with advanced cancer. In malignant disease a cycle of vomiting may exacerbate the rise in serum calcium and these patients often have a hypochloraemic metabolic alkalosis, as opposed to the hyperchloraemic metabolic acidosis seen in hyperparathyroidism.

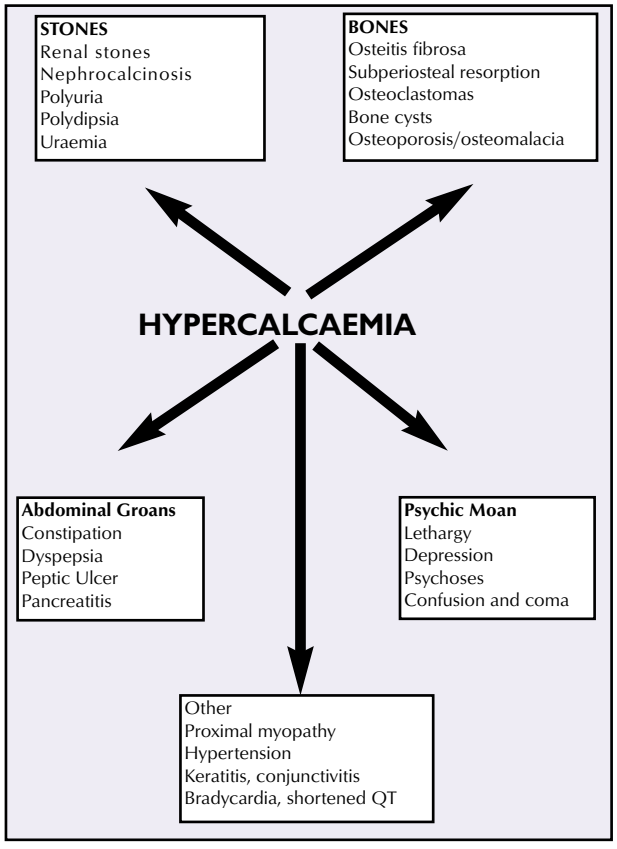

Figure 2 Complications of hypercalcaemia

Hyperparathyroidism:	Sporadic Familial Associated with MEN 1 or 2a After renal transplantation
Variant-hyperparathyroidism:	Benign hypocalciuric hypercalcaemia Lithium therapy Tertiary hyperparathyroidism in chronic renal failure
Malignancies:	Myeloma Leukaemia Lymphoma Bronchial Carcinoma Bony metastasis (Breast, prostate. etc)
Sarcoidosis or granulomatous disease	
Endocrinopathies:	Thyrotoxicosis Adrenal insufficiency Phaechromocytoma VIPoma Acromegaly
Drug Induced:	Thiazide diuretics Vitamin A Vitamin D Lithium treatment Milk-Alkali Oestrogens, androgens, -tamoxifen
Immobility	
Acute renal failure	

Table 1 Causes of Hypercalcaemia

Hypercalcaemia of malignancy is a potentially life-threatening complication of cancer, usually resulting from increased bone resorption by osteoclasts. In some cases the hypercalcaemia may result from local osteolysis due to metastatic disease or direct bone invasion. The increased osteoclastic activity in malignancy is usually driven by a parathyroid hormone related hormone which is usually elevated in patients with hypercalcaemia of malignancy.[4] Rarely, ectopic parathyroid hormone may be produced by tumours and certain lymphomas may secrete vitamin D.

In patients with breast cancer, hypercalcaemia is associated with a poorer prognosis and lower quality of life.[5]

Familial benign hypocalciuric hypercalcaemia

This condition is inherited in an autosomal dominant manner and is characterised by a mild hypercalcaemia, often accompanied by hypermagnesaemia and hypophosphataemia. Familial benign hypocalciuric hypercalcaemia is caused by a loss of function mutation in the parathyroid calcium receptor. Generally the condition is asymptomatic but chondrocalcinosis, pancreatitis and gallstones may occur. It is often difficult to distinguish from primary hyperparathyroidism. Parathyroid hormone levels are often normal or slightly elevated but the parathyroid glands are of normal size. A low urinary calcium:creatinine ratio is suggestive of the diagnosis, along with a low urinary calcium excretion rate. To confirm the diagnosis family studies must be undertaken.[6]

Drug Induced Hypercalcaemia

Thiazides and other diuretics may cause mild hypercalcaemia beyond that which could be accounted for by haemoconcentration alone. Furthermore, thiazides exacerbate the effect of underlying primary hyperparathyroidism.

Lithium reduces urinary calcium excretion and also reduces the negative feedback effect of a high calcium on PTH production, resulting in elevated PTH and calcium. Up to 10% of patients taking lithium become mildly hypercalcaemic.

Vitamin D intoxication occurs only in patients taking large quantities of Vitamin D. It should be noted, however, that the serum 1,25 hydroxyvitamin D may be normal in these individuals. The diagnosis is established by measuring the serum 25- hydroxy vitamin D, which is often grossly elevated.[15]

Hypercalcaemia due to Vitamin A intoxication is probably due to a direct effect of Vitamin A on bone resorption. Treatment with corticosteroids is usually effective.

The Milk-alkali syndrome

Ingestion of large quantities of absorbable antacids containing calcium may result in hypercalcaemia with alkalosis, renal impairment and often nephrocalcinosis. This is known as the milk-alkali syndrome and has reduced in incidence following the introduction of H2-antagonists and proton pump inhibitors.

Immobility

Hypercalcaemia secondary to immobility tends to occur in patients with pre-existing increased bone turnover (adolescents, Paget's, and thyrotoxicosis). The disorder usually resolves spontaneously with the restoration of activity, but bisphosphonates can be used if necessary.

Granulomatous Disorders

Vitamin D-dependent hypercalcaemia occurs in granulomatous disorders such as sarcoidosis, tuberculosis, fungal granulomas, berylliosis and lymphomas. The hypercalcaemia is due to an abnormality of 1,25-hydroxyvitamin D production in the the granulomata. In this group of disorders, PTH is suppressed but uniquely 1,25-hydoxy vitaminD is elevated. This metabolic defect corrects rapidly with corticosteroids.[7]

Management of the hypercalcaemic patient

1. Clinical assessment

Many of the symptoms and signs of hypercalcaemia can be predicted from the complications outlined in figure 2. A high index of suspicion should be maintained when a patient presents in a non-specific manor with any combination of these, particularly in the context in known malignant disease or primary hyperparathyroidism.

If hypercalcaemia has already been confirmed, clinical review should include early assessment of the patient's hydration status, so that measures to correct dehydration can be initiated as soon as possible. After this the history and examination should focus on attempts to identify the cause.

Features which should be actively sought from the history should include: weight loss (malignancy, thyrotoxicosis), bone pain / recent fractures (metastatic disease, myeloma), respiratory symptoms (bronchial malignancy, sarcoid) haematuria / loin pain (renal calculi, renal carcinoma), prostatic symptoms (in men). Careful enquiry should be made about past illnesses, particularly in relation to endocrine, renal or malignant disease, along with a full drug history (including over the counter antacids). A careful family history may point towards the diagnosis of familial hypocalciuric hypercalcaemia.

Examination should include assessment of thyroid status and careful inspection of the neck for evidence of a goitre (Graves disease, thyroid carcinoma). All systems should be thoroughly examined for evidence of underlying malignancy, including all lymph node areas. Rectal examination (with careful assessment of the prostate gland in men) and breast examination in women are mandatory in almost all cases.

2. Investigation

Baseline investigations should involve the measurement of albumin to allow the corrected calcium to be calculated. Many laboratories will automatically provide a 'corrected' calcium value, but the following equation may be used:

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corrected calcium (mmol/l) = uncorrected calcium (mmol/l) + 0.02 x (40 – albumin)

A full list of suggested investigations, together with justification for each, is shown in table 2.

Parathyroid Hormone (PTH) should be measured simultaneously with serum corrected calcium before commencing specific treatments for hypercalcaemia. Most laboratories require a fresh sample for analysis, so measurement during laboratory 'working hours' and a telephone call to the biochemist before dispatching the sample may be advisory. If available, measurement of PTH related protein (PTH-rp) may assist in the diagnosis of a cause of hypercalcaemia of malignancy. An elevated PTH-rp makes the diagnosis more likely but a normal level does not exclude malignancy.[8] A serum calcium of >3 mmol/l also makes the diagnosis of malignancy more likely.[9]

If PTH is elevated, imaging of the parathyroid glands is required by Sestamibi subtraction scanning or ultrasound with a view to definitive surgical treatment.

3. Treatment

Severe hypercalcaemia may be life threatening and requires prompt treatment to control symptoms and to prevent the development of irreversible organ damage. Having treated the acute elevation in calcium the underlying cause of the hypercalcaemia must be sought and, if possible, removed.

Initial Management

The initial management of the hypercalcaemic patient involves rehydration and evaluation of underlying cause. Initial treatment is to rehydrate the patients with 2-3 litres N-Saline per day for 48 hours. A loop diuretic can then be given to increase calcium excretion and avoid fluid overload in patients with congestive cardiac failure.[10] Once rehydration has begun and samples taken for PTH levels, treatment should be aimed at increasing urinary calcium excretion and inhibiting bone resorption of calcium.

The specific therapies to reduce calcium are bisphosphonates, corticosteroids, and gallium nitrate as discussed below. Frusemide induced diuresis, mithramycin, non-steroidal anti-inflammatory drugs and calcitonin, may occasionally be useful in patients who do not respond to initial treatment measures.[11]

Bisphosphonates

Bisphosphonates were first used in the 1930s as anti-scaling and anti-corrosion agents in industry. First generation bisphosphonates (etidronate and clondronate) were introduced to medical practice nearly 30 years ago. These have largely been superseded by second generation nitrogen-containing bisphosphonates (Pamidronate, alendronate, zoledronate).

Bisphosphonates are potent inhibitors of osteoclastic bone resorption (see Table 2 next page).

Intravenous pamidronate is currently the drug treatment of choice for hypercalcaemia.[12] When used in conjunction with rehydration, pamidronate accelerates the return to normocalcaemia and reduces relapses. The effect of pamidronate is dose dependent.[13] However it should be remembered that the calcium concentration may continue to fall for 5 days after bisphosphonate treatment. Potent sustained effects on bone resorption result in a long duration of action (12-30 days).[14] Calcium levels return to normal in over 90% of patients with malignancy-associated hypercalcaemia following a 90mg infusion of pamidronate.[15]

Pamidronate has been shown to be more effective in the treatment of hypercalcaemia than clodronate. Significantly more patients treated with pamidronate achieved normocalcaemia and the duration of effect was longer.[16] Furthermore, significantly fewer patients suffer from gastrointestinal side-effects with pamidronate, which is also less nephrotoxic. However second generation bisphosphonates are associated with an acute phase reaction with reports of flushing and pyrexia in up to 16% of patients.[17]

Zolendronic acid is a new bisphosphonate and has been show to have superior efficacy to pamidronate with no significant difference in side effects.[18] Zolendronic acid has the added advantage of being infused over 5 minutes rather than 30-90 minutes required for a pamidronate infusion.

Bisphosphonates may also have a role in the prevention of hypercalcaemia in multiple myeloma and metastatic breast cancer.[19]

Corticosteroids

Corticosteroids are of use in vitamin D-dependent hypercalcaemia and granulomatous disorders.

There is some evidence to suggest that corticosteroids, used in conjunction with rehydration, are superior to rehydration alone in the treatment of severe hypercalcaemia in breast cancer.[20]

Other treatments

Calcitonin rapidly reduces serum calcium but its short duration of action, frequently reported side effects and the risk if tachyphylaxis limits its use.[21] **Mithramycin** is less effective than bisphosphonate treatment, and its use is limited by adverse side effects, particularly bone marrow suppression, blood clotting abnormalities and platelet dysfunction.[22]

Gallium Nitrate increases excretion of calcium by inhibiting tubular resorption of calcium and is therefore of use in non-PTH dependent hypercalcaemia of malignancy.[23] It requires repeated intravenous infusion for 3 to 5 days and is less effective than pamidronate.[15]

Surgical treatment for hyperparathyroidism

A detailed discussion of the indications for parathyroid surgery in patients with primary hyperparathyroidism is beyond the scope of this article. Such criteria are somewhat contentious. Serum calcium of greater than 3.0 mmol/l, reduced creatinine clearance, recurrent urinary calculi, osteoporosis and a young age (less than 50years) are commonly considered indications for surgery.

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Investigation	Justification	Comments
Full Blood Count Urea, and electrolytes	Assessment of hydration/ renal function	
Liver function	Evidence of malignancy ALP elevated in bony malignancy – isoenzymes can help to identify source	
Thyroid function	Thyrotoxicosis associated with hypercalcaemia	
Parathyroid hormone	Evidence of primary hyperparathyroidism	Lab may require fresh sample - telephone before sending blood
Prostate specific antigen (in males)	Prostate cancer is common cause of bony metastasis, in which case PSA is almost always elevated	
Erythrocyte Sedimentation Rate (ESR)	Usually elevated in myeloma, and in presence of bony metastases	
Serum protein electrophoresis Urinary Bence-Jones protein	Evidence of myeloma (unlikely in presence of normal ESR)	Await result of ESR and PTH before requesting
Chest radiograph	Evidence of bronchogenic malignancy, metastatic disease or sarcoidosis	
Electrocardiograph	Arrhythmias and shortening of the QT interval are recognised features of hypercalcaemia	If abnormal, keep patient on cardiac monitor until calcium level corrected
24-hour urinary calcium	Low in familial hypocalciuric hypercalcaemia	Check other results (above) first before requesting this.
Radionucleotide bone scan	Evidence of bony metastases	Not indicated in myeloma – skeletal survey may be necessary in this case

Table 2 Investigation of patients with hypercalcaemia

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