

The Diagnosis and Management of Hypercalcaemia

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Abstract

Introduction: Hypercalcaemia is a relatively common clinical problem with a wide spectrum of presentations. This review provides an overview of the diagnosis and management of hypercalcaemia, and recent developments in drug therapy. **Methods:** A non-systematic review of the English-language literature on various aspects in the management of hypercalcaemia was conducted. **Results:** Increasingly, more patients with asymptomatic or minimally symptomatic disease are being detected. Appropriate evaluation of hypercalcaemia requires a careful elucidation of the underlying causes, the commonest being primary hyperparathyroidism and malignancy. The decision to treat and extent of treatment depends on factors such as the degree of hypercalcaemia, severity of symptoms, and the underlying cause. Several options are readily available to lower serum calcium levels. In the setting of acute, symptomatic hypercalcaemia, general measures such as saline rehydration and loop diuretics, and more specific measures including bisphosphonates (e.g. clodronate, pamidronate, ibandronate and zoledronate), calcitonin, mithramycin, gallium, glucocorticoids and dialysis, could be utilised. Definitive correction of the underlying cause, such as surgery for primary hyperparathyroidism or anti-tumour therapy, is important in controlling chronic hypercalcaemia. Medical therapy (estrogen, alendronate and raloxifene) is available to control bone sequelae in asymptomatic, mild hyperparathyroidism where surgery is not indicated. **Conclusion:** The therapeutic approach to hypercalcaemia should be tailored to the clinical setting. Developments in the understanding of the pathophysiological processes and the increasing availability of more powerful therapeutic options would help in achieving good outcomes in the management of acute and chronic hypercalcaemia.

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Introduction

Hypercalcaemia is a relatively common clinical problem with the widespread use of routine biochemical screening.^{1,2} Population studies have suggested a prevalence of 3% in women and <1% in men above the age of 60 years.³ The clinical presentation varies from an asymptomatic biochemical abnormality, through symptomatic disease to a life-threatening medical emergency, and this determines to a large extent the therapeutic measures that might be utilised in managing this problem. Increasingly, more patients with asymptomatic or minimally symptomatic disease are being detected, and the body of data on more conservative management options is increasing. This review summarises the diagnosis and management of the clinical spectrum of hypercalcaemia.

Pathophysiology

Calcium has two major roles: it provides structural integrity in the skeleton, and is critically important in the maintenance and control of major biochemical processes. The concentration of calcium in extra- and intracellular fluids is maintained with great accuracy. Calcium is

distributed in 3 major fractions: the ionized portion (~50%) which is physiologically important; the protein-bound portion (~40%), most of which is bound to albumin; and a complexed portion (~10%) linked mainly to citrate, or sulphate.⁴ Under normal circumstances, the plasma calcium concentration reflects a balance between the flux of calcium between the extracellular fluid and the intracellular fluid, skeleton, gastrointestinal tract, kidney and skin. This calcium flux is regulated by parathyroid hormone (PTH), 1,25-dihydroxyvitamin D (1,25(OH)₂D) and calcitonin. The normal serum total calcium level ranges between 2.1 and 2.6 mmol/L.

In response to hypercalcaemia, the secretion of PTH decreases, and this impacts on several target organs. Calcium and phosphate mobilisation from the bone decreases, as do calcium reabsorption from the distal renal tubules, urinary phosphate excretion and synthesis of 1,25(OH)₂D. The latter in turn decreases the efficiency of calcium and phosphorus absorption in the intestine. Whether the putative effects of calcitonin in counter-regulating PTH are of pathophysiologic importance in humans remains unclear. PTH-mediated distal tubular calcium reabsorption and

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osteoclastic bone resorption are the major control points in minute-to-minute serum calcium homeostasis, with the former being quantitatively more important. Maximal adjustments to the rate of calcium absorption in the intestine via the PTH-1,25(OH)₂D axis require 24 to 48 hours to become fully operative.

Hypercalcaemia results when the entry of calcium into the circulation exceeds the excretion of calcium into the urine or deposition in bone. The limiting factor in the system's defence against hypercalcaemia is the capacity of the kidneys to excrete calcium.

'Factitious' hypercalcaemia may occur with severe dehydration and volume contraction, where there is relative hyperalbuminaemia. As about half of the calcium in serum is bound to protein, principally albumin, an elevated serum total calcium concentration without any rise in the serum ionized calcium concentration may occur, the patient actually being eucalcaemic.

Clinical Manifestations

With the widespread use of routine biochemical screening, more patients will present with an asymptomatic biochemical abnormality or minimally symptomatic disease. In symptomatic individuals, the symptoms and signs associated with hypercalcaemia may broadly be attributed to the elevation in the serum calcium concentration or to the underlying disease.

Symptoms

Although hypercalcaemia can affect a variety of organ systems (Table I), the most common symptoms are relatively nonspecific.¹ These include fatigue, weakness, anorexia, depression, vague abdominal pain, and constipation, seen in 30% to 75% of patients, which often resolve with reversal of hypercalcaemia.² The extent of symptoms is a function of both the degree and the rate of onset of the elevation in the serum calcium concentration. Thus, a serum calcium of 3 to 3.5 mmol/L may be well tolerated chronically while an acute rise to these concentrations may cause marked changes in sensorium.

The most common neuropsychiatric symptoms have been anxiety, depression, and cognitive dysfunction (~50% of patients).³ Improvement in some or all of these symptoms has been described after correction of the hypercalcaemia but these usually uncontrolled reports are difficult to evaluate. More severe symptoms tend to occur in patients with marked hypercalcaemia and/or elderly patients.⁵ Personality changes and affective disorders have been described at serum calcium concentrations above 3 mmol/L, while confusion, organic psychosis, hallucinations, somnolence, and coma tend to be rare in otherwise healthy patients until the serum calcium

TABLE I: CLINICAL FEATURES OF HYPERCALCAEMIA

Gastrointestinal
Constipation, vague abdominal pain
Nausea, vomiting, anorexia
Thirst, dry mouth, polydipsia, dehydration
Peptic ulcer disease, pancreatitis
Genitourinary
Polyuria, nocturia, renal tubular dysfunction
Nephrolithiasis, nephrocalcinosis
Acute and chronic renal insufficiency, uremia
Neuropsychiatric
Fatigue, lethargy
Cognitive dysfunction, depression, anxiety, irritability
Psychosis, dementia
Headache, blurred vision
Drowsiness, confusion, stupor, coma, hyporeflexia
Corneal or conjunctival calcification
Musculoskeletal
Muscle weakness
Gout, pseudogout, chondrocalcinosis
Arthralgia, bone pain, osteoporosis
Cardiovascular
Hypertension
Calcification in aortic and mitral valves, and myocardium
ECG changes: short QT, arrhythmia, cardiac arrest
Asymptomatic

concentration is above 4 mmol/L.

Constipation is the most common gastrointestinal complaint (~33%) in patients with hypercalcaemia of any aetiology.⁶ Anorexia and vague abdominal complaints are also common symptoms. Occasionally, severe hypercalcaemia leads to acute pancreatitis.

Nephrolithiasis occurring in patients with long-standing hypercalcaemia is predominantly due to primary hyperparathyroidism. Nephrolithiasis has been reported in up to 20% of patients with hyperparathyroidism, while 4% to 5% of stone formers have hyperparathyroidism.⁷ Chronic hypercalcaemia leads to a defect in concentrating ability that may induce polyuria and polydipsia in up to 20% of patients. The development of renal insufficiency in primary hyperparathyroidism is related to the degree and duration of hypercalcaemia. Mild hypercalcaemia is only rarely associated with renal insufficiency. Higher elevations in the serum calcium concentration (3 to 3.75 mmol/L) can lead to a reversible fall in the glomerular filtration rate mediated by renal vasoconstriction and volume contraction.⁸ Long-standing hypercalcaemia and hypercalciuria lead to the development of chronic hypercalcaemic nephropathy, which may be irreversible and continue to progress despite the control of hypercalcaemia.

Profound muscle weakness was prominent in the original description of hypercalcaemic patients with hyperpara-

thyroidism, unlike in the majority of patients today who are diagnosed earlier in the course of the disease. Most would be asymptomatic, but mild weakness may be detected if actively sought.^{3,9} Arthralgia and bone pain may occur, related to skeletal involvement by the underlying disease. The classical skeletal manifestation of primary hyperparathyroidism, osteitis fibrosa cystica, is now rare. Radiographically, subperiosteal resorption of the distal phalanges and clavicles, 'salt and pepper' appearance of the skull, bone cysts and brown tumours of the long bones, are less seen as compared with low bone density. Malignant involvement of bone may give rise to pain symptoms.

Hypertension may occur with increased frequency in patients with hypercalcaemia, possibly related to renal insufficiency and calcium-induced vasoconstriction. The elevation in blood pressure may or may not resolve with surgical cure of the hyperparathyroidism.¹⁰ Calcium deposition may occur in various structures of the heart.¹¹ Shortening of the QT interval, bradycardia and first-degree atrioventricular block may be found on ECG.

Physical Findings

There are usually no specific physical findings of hypercalcaemia other than those related to an underlying disease such as malignancy. Band keratopathy is a very rare finding in patients with hypercalcaemia. The subepithelial calcium phosphate deposits extend as a horizontal band across the cornea in the area that is exposed between the eyelids, and is usually detected by slit-lamp examination.

Aetiology

Hypercalcaemia is, in almost all patients, due to an elevation in the ionized (or free) calcium concentration. The major causes of hypercalcaemia are hyperparathyroidism and malignancy, accounting for 80% to 90% of all hypercalcaemic patients.¹² Table II elucidates the differential diagnosis of hypercalcaemia. Hyperparathyroidism is the most common cause in ambulatory patients, accounting for 60% of cases,¹² as it is unusual for the malignancy not to be clinically apparent when hypercalcaemia is first noted. However, among hospitalised patients, cancer is the most common cause, accounting for about 65% of cases, while hyperparathyroidism accounts for another 25%.^{12,13}

Primary hyperparathyroidism occurs at all ages but is most frequent in the sixth decade of life, the majority occurring in postmenopausal women in a ratio of 3:1 compared to men.¹⁴ The cause of hyperparathyroidism is one or more hyperfunctioning glands: solitary adenomas account for 80% of patients; hyperplasia involving all parathyroid glands accounts for 15% to 20% and these may

TABLE II: DIFFERENTIAL DIAGNOSIS OF HYPERCALCAEMIA

More common
Primary hyperparathyroidism
Malignancy-associated
Associated with chronic renal failure (multifactorial)
Vitamin D analogue or vitamin D therapy
Less common
Miscellaneous: Immobilisation, dehydration, total peripheral nutrition
Granulomatous diseases: sarcoidosis
Drugs and minerals: milk-alkali syndrome, thiazides, lithium, aminophylline, aluminium toxicity, vitamin A intoxication
Endocrine disorders: thyrotoxicosis
Rare
Endocrine disorders: pheochromocytoma, acromegaly, acute adrenal insufficiency
Granulomatous diseases: tuberculosis, histoplasmosis, leprosy
Miscellaneous: hypophosphatasia, familial benign hypocalciuric hypercalcaemia

be hereditary or associated with other endocrine abnormalities; 2% have double or multiple adenomas and <1% have carcinoma.¹⁵ Excessive parathyroid hormone production in primary hyperparathyroidism results in activation of osteoclasts via stimulation of osteoblasts, leading to increased bone resorption and hypercalcaemia.

Activation of osteoclasts leading to increased bone resorption is also the main cause of hypercalcaemia in malignancy. The production of humoral osteoclast activators, particularly PTH-related protein (PTH-rP), is seen with squamous cell carcinomas and genitourinary cancers, and accounts for around 80% of cases of malignancy-associated hypercalcaemia.¹⁶ Local resorption of bone induced by metastases (mediated by local release of cytokines such as tumour necrosis factor and interleukin-1) occurs with multiple myeloma, breast cancer and lymphoma, and accounts for 20% of cases. In contrast, tumoural calcitriol production may cause hypercalcaemia in patients with Hodgkin's disease or non-Hodgkin's lymphoma, accounting for 1% of cases. Tumours producing PTH ectopically are extremely rare.

Renal failure per se is usually not associated with hypercalcaemia because of the calcium-lowering effects of concurrent hyperphosphataemia and decreased calcitriol synthesis. However, hypercalcaemia may be seen in patients who are given calcium compounds to bind dietary phosphate, as well as vitamin D analogues in an attempt to reverse both hypocalcaemia and secondary hyperparathyroidism in chronic renal failure.¹⁷ Other problems which contribute to hypercalcaemia in renal failure patients include immobilisation, dehydration, tertiary hyperparathyroidism and aluminium intoxication. As many as 50% (81 of 162) of hospitalised patients with hyper-

calcaemia were reportedly associated with chronic renal failure.¹⁸

Excessive intake of vitamin D or especially its analogues may cause hypercalcaemia by increasing calcium absorption and bone resorption. A high calcium intake alone is a rare cause of hypercalcaemia, because the initial elevation in serum calcium concentration inhibits both the release of PTH and the synthesis of calcitriol. However, an increasingly recognised cause of hypercalcaemia is the milk-alkali syndrome due to the excessive use of calcium carbonate to treat osteoporosis and dyspepsia.¹⁹ Individual susceptibility is probably an important factor here as the majority of individuals treated with calcium carbonate do not develop hypercalcaemia.¹⁹

Chronic granulomatous disorders such as sarcoidosis, tuberculosis, as well as malignant lymphomas may cause hypercalcaemia by increased endogenous production of calcitriol. Complete, prolonged bed rest due to orthopaedic or neurological disorders may lead to accelerated bone resorption and hypercalcaemia within days to weeks in individuals whose underlying rate of bone turnover is high.²⁰

Thiazide diuretics lower urinary calcium excretion but rarely cause hypercalcaemia in otherwise normal persons unless an underlying increase in bone reabsorption such as those with hyperparathyroidism is present. Chronic lithium therapy is believed to result in mild hypercalcaemia due to increased secretion of PTH resulting from an increase in the set point at which calcium suppresses PTH release. Mild hypercalcaemia has been reported in as many as 47% of patients with hyperthyroidism.²¹

Familial benign hypocalciuric hypercalcaemia (FBHH) is a rare autosomal dominant disorder in which the primary defect is a loss-of-function mutation in the calcium ion-sensing receptor (CaR) on the parathyroid cells and in the kidneys.²² These mutations have been found primarily in the extracellular and transmembrane domains of the CaR. The result is a set-point abnormality, with reduced feedback-responsiveness of PTH secretion to calcium. It is characterised by lifelong, mild, benign hypercalcaemia, hypocalciuria, normal to slightly increased serum PTH concentrations, and the absence of most of the usual complications associated with hypercalcaemia.²²

Diagnostic Approach

For clinical purposes, the total calcium concentration is the most widely evaluated index of calcium status, although the ionized calcium concentration provides a more precise estimate, particularly in critically ill patients with decreased serum protein levels, acid-base disturbances or those who have received large volumes of citrated blood products. Although technically more difficult with several sources of

possible errors, measurement of ionized calcium is becoming more widely available. The normal range varies depending on the technique used, the nature of the specimen, whether serum, plasma or heparinised whole blood, and the type of collection tube.

Normal values for serum total calcium vary somewhat among clinical laboratories, but in general, range from 2.1 to 2.6 mmol/L. For routine clinical interpretation, the total serum calcium concentration (in mmol/L) is corrected for albumin concentration (in g/L) as follows: corrected serum calcium = measured calcium + 0.02 (40 - serum albumin). A single raised serum calcium value should be repeated to confirm the diagnosis, together with serum phosphate and intact parathyroid hormone levels. Table III and Figure 1 show the diagnostic approach to hypercalcaemia using these assays as a basis for evaluation, with further tests suggested to clarify the diagnosis. Because primary

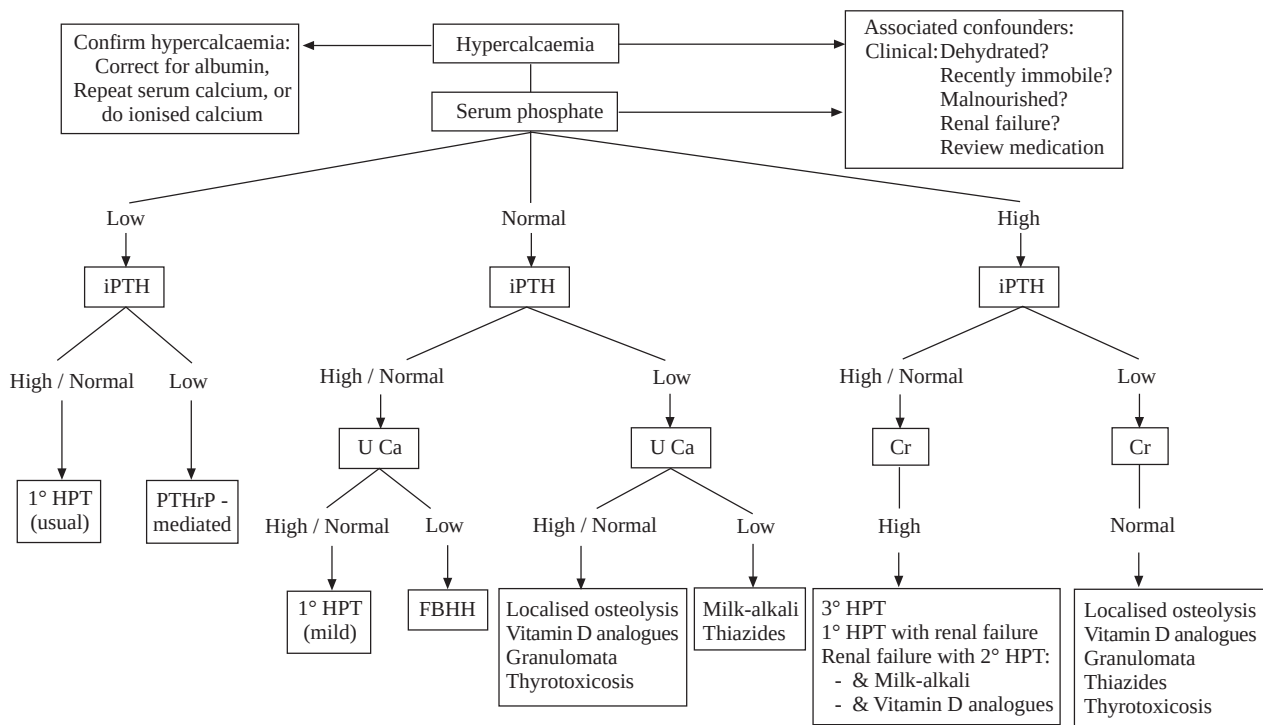
TABLE III: DIAGNOSTIC APPROACH TO HYPERCALCAEMIA: LABORATORY EVALUATION

Problem	Ca ²⁺	PO ₄	iPTH	Other typical findings
PTH-mediated	↑ / ↑↑ ↓ / N	↑ / N	HCO ₃ ↓, Cl↑, U Ca ↑ / N	
PTHrP-mediated	↑↑	↓	↓	CXR, ENT / GI / GU screen, Cl↓, U Ca ↑↑
Local osteolysis	↑↑	N	↓	Myeloma / lymphoma screen, Cl↓, U Ca ↑↑
Vitamin D-mediated, e.g. granuloma, supplements	↑	N / ↑	↓	CXR, review medications, Cl↓, U Ca ↑↑ 25(OH)D ↓ / ↑(see text)
FBHH	↑	N	↑ / N	U Ca ↓↓
Thyrotoxicosis	↑	N / ↑	↓	Free T ₄ ↑↑, TSH↓↓; U Ca ↑
Milk-alkali syndrome	↑	↑ / N	↓	HCO ₃ ↑, Cl↓, U Ca ↓
Thiazide use	↑	N / ↑	↓	Na↓, K↓, U Ca ↓
Tertiary hyperparathyroidism	↑	↑	↑	Cr ↑

Co-existing problems may affect serum calcium and phosphate levels in opposing directions to the primary disease, altering the typical relationships between these three components as described above. These problems must be considered, and include:

1. Dehydration Ca ↑, PO₄ N / ↑
2. Immobilization Ca ↑, PO₄ N
3. Poor nutrition state Ca ↓, PO₄ ↓
4. Renal dysfunction Ca ↓ / N, PO₄ ↑

(where N normal, ↑ increase, ↓ decrease, Ca calcium, PO₄ phosphate, iPTH intact parathyroid hormone, PTHrP parathyroid hormone-related peptide, 25(OH)D 25-hydroxyvitamin D, FBHH familial benign hypocalciuric hypercalcaemia, Na sodium, K potassium, Cl chloride, HCO₃ bicarbonate, Cr creatinine, free T₄ free thyroxine, TSH thyroid stimulating hormone, U urinary, ENT ear, nose & throat, GI gastrointestinal, GU genitourinary, CXR chest radiograph)



For additional tests, refer to Table III.

(1°, 2° & 3° HPT: primary, secondary and tertiary hyperparathyroidism; PTHrP: parathyroid hormone related peptide;

FBHH: familial benign hypocalciuric hypercalcaemia)

Fig. 1. Algorithm for initial diagnostic approach to hypercalcaemia.

hyperparathyroidism and malignancy account for the majority of cases, more involved diagnostic investigations should be undertaken only after these have been excluded.

It is estimated that history, physical examination, chest X-ray (looking for malignancy or sarcoidosis), and laboratory data (including serum protein electrophoresis for possible multiple myeloma) will provide the correct diagnosis with an accuracy of 95%.¹² Addition of an assay for intact PTH (iPTH) will increase the accuracy to 99%.

In malignancies, manifestations of the underlying disease are usually clinically obvious. Hypercalcaemia may be noted incidentally in the work-up of the malignancy. Occasionally, an occult tumour gives rise to hypercalcaemia and the clinical picture may resemble primary hyperparathyroidism. Chronicity of hypercalcaemia, such as over periods of a year, usually excludes malignancy. The degree of hypercalcaemia may be useful diagnostically: the hypercalcaemia of primary hyperparathyroidism is often milder with serum calcium concentrations below 2.75 mmol/L, whereas values above 3.25 mmol/L should lead to active evaluation for malignancy. Ten to 20% of patients with primary hyperparathyroidism have a serum PTH concentration in the upper end of the normal range which is considered inappropriate in the presence of hypercalcaemia.

Other available assays such as 25-hydroxyvitamin D (25(OH)D) and bone turnover markers have limited use in the evaluation of hypercalcaemia. The 25(OH)D assay may be useful in diagnosing hypervitaminosis D due to the ingestion of either vitamin D or calcidiol itself, but not in cases related to vitamin D analogue ingestion. Levels of 25(OH)D are reduced and 1,25(OH)₂D increased in disorders with enhanced 25(OH)D to 1,25(OH)₂D conversion such as granulomatous disease and primary hyperparathyroidism. Bone turnover markers may suggest a high bone turnover state as seen with PTH- and PTHrP-driven hypercalcaemia. Typically, 60% to >80% of all patients with malignancy-associated hypercalcaemia have increased PTHrP values,¹³ whether using the N-terminal, mid-region or two-site immunometric assay. PTHrP measurements may have some role in monitoring response to treatment of the primary tumour, or predicting the response to calcium-lowering agents and survival, higher levels bearing a worse prognosis in both instances.²³ However, the PTHrP and 1,25(OH)₂D assays are currently unavailable in Singapore.

Treatment

The decision to institute therapy and the choice of therapy would depend on several factors such as the level

of serum calcium, presence of symptoms, and the underlying cause of hypercalcaemia,^{24,25} in relation to the various clinical settings ranging from acute, life-threatening hypercalcaemia to chronic, asymptomatic hypercalcaemia.

General measures such as hydration and calciuresis may suffice in patients with mild to moderate, asymptomatic hypercalcaemia (where serum calcium levels are usually <3.0 mmol/L, but occasionally higher).²⁴⁻²⁶ Specific measures such as bisphosphonates, calcitonin or glucocorticoids may be considered in patients with serum calcium >3.0 to 3.5 mmol/L, especially when the hypercalcaemia is symptomatic.²⁴⁻²⁶ Some authors recommend treating patients with asymptomatic hypercalcaemia in the range of 2.8 to 3 mmol/L when there is associated hypercalciuria because of the risk of nephrolithiasis and nephrocalcinosis. The presence of advanced malignancy with no definitive treatment plans and grave prognosis may temper the decision on measures employed.²⁵

The basic goals of therapy for hypercalcaemia are to correct dehydration, to lower the serum calcium concentration (by enhancing renal excretion of calcium and inhibiting accelerated bone resorption) and, where possible, to correct or decrease the underlying disease, such as parathyroidectomy in patients with primary hyperparathyroidism or anti-tumour therapy in patients with cancer-associated hypercalcaemia.^{24,26} Table IV summarises the treatment options available for patients with acute, severe hypercalcaemia.

General Measures

Hydration

The first step in the management of severe hypercalcaemia (serum calcium >3 mmol/L) is volume re-expansion. This enhances renal calcium clearance by increasing filtration

of calcium, reducing renal tubular sodium and calcium reabsorption, and causing obligatory calciuresis. Serum calcium may decline by ~0.5 mmol/L. The rate of administration of isotonic saline should be based on the severity of the hypercalcaemia, the extent of dehydration, and the tolerance of the cardiovascular system for volume expansion. A typical fluid regimen comprises 2.5 to 4 L of isotonic saline daily, unless the patient has heart failure or renal failure.

Calciuresis

A loop diuretic (e.g. frusemide, 20 to 40 mg intravenously every 2 to 12 hours) can be added once hypervolaemia-induced natriuresis has been induced, and this may help guard against volume overload. The patient should be monitored carefully to prevent recurrent hypovolaemia, which will limit the calciuresis.

Specific Measures

General measures may reduce serum calcium concentrations appreciably, but do not impact on excessive mobilisation of calcium from bone, which is the pathogenetic process in the majority of cases. If serum calcium remains above 3.0 mmol/L after adequate saline/loop diuretic therapy, specific therapy should be implemented. There is currently no longer any role for intravenous phosphate in the management of acute hypercalcaemia.

Bisphosphonates

The bisphosphonates are relatively nontoxic compounds that are more potent than intravenous saline and are very effective in patients with moderately severe hypercalcaemia. Their maximum effect occurs in two to four days. Clodronate, pamidronate, ibandronate and zoledronate are currently available for the treatment of hypercalcaemia.

TABLE IV: THERAPY FOR ACUTE HYPERCALCAEMIA

Treatment	Dose	Onset	Duration (days)	Response (%)
Increase urinary calcium excretion				
Saline	-	2-4 hours	1-2	0-10
Saline + loop diuretic	-	2-4 hours	1-2	0-10
Decrease bone resorption				
Clodronate	300 mg/day x 5 days	1-2 days	10-14	~ 80
Pamidronate	90 mg	1-2 days	11-28	70-90
Ibandronate	4-6 mg	1-2 days	18-26	70-80
Zoledronate	4-8 mg	1-2 days	32-43	~ 90
Calcitonin	4-8 IU/kg q6-12h	4-6 hours	2-3	60-70
Mithramycin	25 mg/kg	1-2 days	5-7	40-60
Gallium nitrate	200 mg/m ² /day	2-3 days	10-14	70-80
Decreased intestinal calcium absorption				
Corticosteroids, e.g. prednisolone	40-60 mg/d	2-5 days	-	-
Exchange with extracorporeal calcium pool				
Dialysis	-	hours-days	-	-

Clodronate is given intravenously (300 mg/day in 500 ml isotonic saline or dextrose 5% over 4 hours) for at least 5 consecutive days when used in the treatment of hypercalcaemia.²⁷ A single-day infusion of 1500 mg in 500 ml isotonic saline over 4 hours has been shown to be as effective.²⁸ Once achieved, normocalcaemia may be maintained on oral clodronate 800 to 1600 mg bd.

Pamidronate is more potent than clodronate with longer-lasting hypocalcaemic effects,²⁹ and is given as a single intravenous infusion of 60 to 90 mg in 500 ml isotonic saline over 4 hours.³⁰ The dose should not be repeated until after a minimum of seven days. The response to pamidronate is often sustained for up to two to four weeks, with an average maintenance of normocalcaemia of 15 days. In hypercalcaemia of malignancy, the incidence of recurrent hypercalcaemia was 50% when pamidronate was administered once every three weeks versus only 10% with administration every two weeks.³¹ Pamidronate is well-tolerated, with a small incidence of fever being the main side effect. Although it is excreted by the kidney, pamidronate seems to be safe and effective for the treatment of dialysis patients who have severe hypercalcaemia induced by the combination of calcium carbonate and calcitriol.³² In such patients, it has been recommended that the pamidronate dose not exceed 30 mg. It has also been used successfully in usual doses in patients with hypercalcaemia related to renal insufficiency³³ and immobilisation.³⁴

Ibandronate is a newer bisphosphonate which is given as a single intravenous infusion of 4 to 6 mg in 500 ml isotonic saline over 4 hours. In a study involving a total of 147 patients with tumour-induced hypercalcaemia, a single dose of ibandronate (4 or 6 mg) normalised the corrected serum calcium level in 75% of patients.³⁵ In some patients, normocalcaemia lasted up to 36 days.

Zoledronate is another promising bisphosphonate given as a 5-minute infusion. In a study involving 287 patients with hypercalcaemia of malignancy, single doses of zoledronate (4 and 8 mg) and pamidronate 90 mg normalised serum calcium in 88%, 87% and 70% by day 10, respectively, and maintained normocalcaemia for 32, 43 and 18 days, respectively.³⁶

Calcitonin

Salmon calcitonin (4 to 8 IU/kg) is given intramuscularly or subcutaneously every 6 to 12 hours. It is safe and nontoxic. When effective, it rapidly lowers serum calcium concentration, beginning within two to six hours, albeit by a modest degree of up to 0.5 mmol/L, and for a relatively transient duration of 1 to 3 days.²⁴ Simultaneous administration of glucocorticoids may enhance and prolong the effectiveness of calcitonin. There is an additive effect when calcitonin is given with a bisphosphonate.²⁶

Mithramycin and Gallium Nitrate

These drugs are invariably mentioned in most articles on this subject, but are seldom used as they are not readily available. They are toxic and extensive experience with them is lacking.

Mithramycin (25 µg/kg) is given intravenously over three to six hours.²⁶ Serum calcium concentrations begin to fall within about 12 hours, usually reaching a nadir by 48 hours. The hypocalcaemic effect lasts for several days; repeated doses can be given at 3- to 7-day intervals. Despite its reliability and efficacy, mithramycin is toxic, particularly in patients with liver, bone marrow, or kidney disease, and is therefore rarely used.

Gallium nitrate is another drug that can inhibit bone resorption and lower serum calcium concentrations.²⁶ It has an additional effect in vitro to inhibit PTH secretion; it may therefore be particularly effective in the treatment of hypercalcaemia due to hyperparathyroidism. However, gallium nitrate can be nephrotoxic, usually requires infusion over 5 days, and too little experience is available at present to recommend its routine clinical use.

Glucocorticoids

Glucocorticoids are the therapy of choice for patients with granulomatous diseases and other causes of vitamin D excess such as vitamin D toxicity, and in occasional patients with malignant lymphomas.²⁶ Prednisolone (40 to 60 mg/day) will usually reduce serum calcium concentrations within two to five days by decreasing calcitriol production by the activated mononuclear cells in the lung and lymph nodes. If this is ineffective or not tolerated, chloroquine, hydroxychloroquine, and ketoconazole, which similarly reduce calcitriol production, can be given.

Dialysis

Haemodialysis should be considered, in addition to the above treatments, in patients who have serum calcium concentrations in the range of 4.5 to 5 mmol/L and neurologic symptoms but a stable circulation. Haemodialysis with little or no calcium in the dialysis fluid and peritoneal dialysis (though it is slower) are both very effective modes of therapy for hypercalcaemia. Dialysis is particularly useful in patients with renal insufficiency or congestive heart failure who cannot safely be given intravenous saline.³⁷

Correction of Underlying Disease

Primary Hyperparathyroidism

To date, parathyroid surgery remains the only effective treatment for primary hyperparathyroidism. A consensus conference of the National Institutes of Health concluded

in 1990 that surgery was indicated in patients with: a markedly elevated serum calcium concentration (above 2.85 to 3.0 mmol/L), a previous episode of life-threatening hypercalcaemia, a reduced creatinine clearance (<30% of age-matched normal), the presence of a kidney stone(s) detected by abdominal radiography, a markedly elevated 24-hour urinary calcium excretion (>10 mmol/day), or a substantially reduced bone mass (z-score < -2 S.D.), and in young patients below 50 years of age.³⁸ However, surgery may be recommended for patients without major surgical indications with significant neurobehavioural symptoms not attributable to other causes,³⁹ vertebral osteopaenia, concomitant vitamin D deficiency⁴⁰ and possibly for women at perimenopausal age.⁴¹ Surgery is not only an effective but also a safe treatment for primary hyperparathyroidism, even in patients who are more than 70 years old.⁵

Most preoperative localisation techniques have proven less sensitive and therefore less useful for detecting parathyroid lesions than an experienced surgeon.^{42,43} The success rates for surgery are usually in the order of 90% to 99%.^{15,40,43} The complication rates depend largely on surgical experience, ranging from a 1% to 2% risk of permanent hypocalcaemia with experienced surgeons, up to a 15% to 40% risk with less experienced surgeons.^{15,43} Other complications include recurrent laryngeal nerve injury (1% to 2%), minor complications (1%) and death (0.3%).¹⁵ Patients with persistent or recurrent hyperparathyroidism require re-exploration, and every effort should be made to identify abnormal tissue preoperatively with imaging techniques such as sestamibi scans.⁴⁴ Post-operative complications are higher after re-exploration, with hypocalcaemia occurring in a third of patients, and recurrent laryngeal nerve palsy in 4%.⁴⁴

The decision to defer surgery in asymptomatic individuals with a non-classical presentation remains somewhat controversial.⁴¹ In most patients, mild primary hyperparathyroidism progresses slowly, if at all. However, during a 10-year follow-up period of 121 asymptomatic patients, about 25% had progressive disease, manifesting as a marked hypercalcaemia, low cortical bone mass or marked hypercalcaemia.⁴⁵ In a longitudinal, population-based cohort of over 400 patients with primary hyperparathyroidism, the risk of vertebral, forearm, rib and pelvic fractures was found to be increased among asymptomatic patients.⁴⁶ Survival was also reduced, but mainly among those with high serum calcium levels.⁴⁷

Patients who may not undergo surgery because of a lack of indications, contraindications, declining the procedure or previous unsuccessful surgery should be evaluated clinically, with 6 to 12 monthly measurements of serum calcium, creatinine and parathyroid hormone, and annual cortical and trabecular bone density measurements. Such

patients should be advised to avoid dehydration and to keep their calcium intake at or below 1000 mg per day.

Most long-term medical therapies appear unable to lower serum calcium levels significantly, although several agents such as estrogen,⁴⁸ alendronate,⁴⁹ and raloxifene⁵⁰ may do so marginally. However, these agents appear to be able to improve low bone density, which may be the only manifestation in patients with mild primary hyperparathyroidism. Their effects on fracture reduction remain to be demonstrated. Nevertheless, these drugs are a useful addition for the conservative management of primary hyperparathyroidism. In future, calcium ion-sensing receptor agonists which inhibit the secretion of parathyroid hormone, may be used to control serum calcium levels.⁵¹

Hypercalcaemia of Malignancy

The control of the underlying malignancy is paramount in achieving long-term control of hypercalcaemia. Without this, hypercalcaemia which may be temporised initially by hydration, potent intravenous bisphosphonates, perhaps with calcitonin to accelerate the calcium-lowering effect, invariably recurs and eventually becomes resistant to therapy. More recently, it has been reported that bisphosphonates appear to prevent hypercalcaemia in patients with breast cancer^{52,53} and multiple myeloma,^{54,55} in addition to lowering the incidence of other skeletal complications and symptoms.⁵²⁻⁵⁶

Potential Future Approaches

Osteoprotegerin (OPG) was identified recently and shown to specifically inhibit osteoclast differentiation by acting as a decoy receptor for OPG ligand (OPG-L or RANKL).⁵⁷ OPG-L is believed to be the final common pathway by which multiple hormones and cytokines regulate osteoclast formation. The biological activity of OPG-L is neutralised by binding to OPG. In a murine model of humoral hypercalcaemia of malignancy, OPG prevented and reversed hypercalcaemia.⁵⁸ Studies on humans are ongoing.

Another approach to the therapy of cancer-induced hypercalcaemia is to reduce the release of PTH-related protein. In vitro studies suggest that this can be achieved by the use of non-calcaemic analogues of calcitriol, such as EB1089 and 22-oxacalcitriol.⁵⁹ In a nude mouse model of cancer-associated hypercalcaemia, 22-oxacalcitriol lowered the serum calcium concentration both alone and in combination with a bisphosphonate.⁶⁰ This compound is also being evaluated in the treatment of renal osteodystrophy.

Yet another possible approach to the treatment of primary hyperparathyroidism is the use of calcimimetic agents, such as nocalcin. These drugs bind to the calcium sensing receptor and suppress the release of PTH. Calcimimetic

drugs have been used in primary hyperparathyroidism,⁵¹ haemodialysis patients with secondary hyperparathyroidism,⁶¹ and in a patient with parathyroid carcinoma and refractory hypercalcaemia.⁶²

The induction of antibodies directed against the hormone responsible for cancer-induced hypercalcaemia is another approach. In a patient with hypercalcaemia due to metastatic parathyroid carcinoma, immunisation with synthetic PTH peptides resulted in the production of blocking antibodies, significantly lowering serum calcium concentration.⁶³

Conclusion

Hypercalcaemia is a relatively common clinical problem. The therapeutic approach to hypercalcaemia should be tailored to the clinical setting, with the aims of controlling hypercalcaemia, and finding and instituting therapy for the underlying cause. Developments in the understanding of the pathophysiological processes and the increasing availability of more powerful therapeutic options would help in achieving better outcomes in the management of acute and chronic hypercalcaemia.

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QUESTIONS

1. Clinical aspects of hypercalcaemia:
 - a) an increasing number of patients will be incidentally detected through health screening, and be asymptomatic.
 - b) the commonest symptoms are non-specific, such as fatigue, depression and constipation, and these often resolve with resolution of hypercalcaemia.
 - c) the extent of symptoms depends on the degree and rate of development of hypercalcaemia.
 - d) hyperparathyroidism and hypercalcaemia account for the majority of patients with nephrolithiasis.
 - e) ECG findings of hypercalcaemia include shortened QT interval, bradycardia and first degree atrioventricular block.
2. Aetiology of hypercalcaemia:
 - a) in the majority of ambulatory patients, the commonest cause is malignancy.
 - b) ingestion of large amounts of calcium usually results in hypercalcaemia.
 - c) excessive intake of vitamin D analogues such as calcitriol with calcium supplementation is a common cause.
 - d) the majority of malignancies associated with hypercalcaemia are occult.
 - e) familial benign hypocalciuric hypercalcaemia (FBHH) is caused by a mutation in the calcium-sensing receptor on parathyroid cells.
3. Investigation of hypercalcaemia:
 - a) for routine clinical interpretation, the most widely evaluated index of calcium status is ionised calcium concentration.
 - b) where total serum calcium concentration is used, it should always be corrected for serum albumin level.
 - c) a normal serum intact parathyroid hormone level in the setting of hypercalcaemia excludes hyperparathyroidism.
 - d) the serum intact parathyroid hormone level will usually be elevated in patients with hypercalcaemia of malignancy.
 - e) the commonest x-ray feature of primary hyperparathyroidism is radiographic osteopaenia.
4. Treatment of acute hypercalcaemia:
 - a) intravenous bisphosphonates should be used early in initial treatment because of its potent efficacy.
 - b) hydration with 1 to 2 L of dextrose 5% or isotonic saline would usually lower serum calcium levels.
 - c) as an early general measure, loop diuretics such as frusemide should always be prescribed concomitantly with the initial infusion.
 - d) calcitonin is not effective in achieving long-term control of hypercalcaemia.
 - e) glucocorticoids are effective in controlling hypercalcaemia caused by primary hyperparathyroidism and malignancy.
5. Treatment of chronic hypercalcaemia:
 - a) parathyroid surgery is the only effective treatment for primary hyperparathyroidism.
 - b) all patients with hyperparathyroidism should be advised to have parathyroidectomy.
 - c) parathyroid imaging is an essential part of the work-up for first-time parathyroidectomy to localise the parathyroid lesion.
 - d) patients with primary hyperparathyroidism who are conservatively treated should be followed up with 6 to 12 monthly measurements of serum calcium, creatinine and parathyroid hormone, and annual bone mineral density measurements.
 - e) powerful and effective drugs are available to achieve long-term control of hypercalcaemia of malignancy in patients receiving palliative care.

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