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CLINICAL REVIEW

The diagnosis and management of hypercalcaemia

Salvatore Minisola *professor*, Jessica Pepe *consultant*, Sara Piemonte *consultant*, Cristiana Cipriani *consultant*

Department of Internal Medicine and Medical Disciplines, "Sapienza" Rome University, 00161 Rome, Italy

Hypercalcaemia is a common finding in the setting of primary care,[1] as well as in emergency departments[2] and patients admitted to hospital.[3] Primary hyperparathyroidism and malignancy are the two most common causes of increased serum calcium levels, together accounting for about 90% of all cases.[4] The remaining 10% represent an important figure, and thus the need to consider other disorders in the evaluation of patients with hypercalcaemia. This review aims to give an overview of the diagnosis and clinical management of hypercalcaemia for non-specialist clinicians and health professionals.

What is the definition of hypercalcaemia?

Hypercalcaemia is diagnosed when the concentration of serum calcium is 2 standard deviations above the mean of values found in people with normal calcium levels, in at least two samples at least one week apart over a period of three months. The serum concentration of total calcium in adults usually ranges between 2.15 and 2.60 mmol/L (8.6-10.4 mg/dL; 4.3-5.2 mEq/L). About 45% of calcium in blood is bound to plasma proteins, particularly albumin, and approximately 10% is bound to anions such as phosphate and citrate; free or ionised calcium (normal values 1.17-1.33 mmol/L) represents about 45% of total calcium. Although the ionised fraction of calcium is the one readily available for activating cellular processes, measurement of total serum calcium is mostly requested in clinical practice. However, when the serum protein concentration fluctuates, the total serum calcium level may vary accordingly, while ionised calcium remains stable. Total serum calcium can then be derived from the formula: total calcium concentration(mmol/L)+0.02(40−serum albumin concentration(g/L).

Changes in blood pH can alter the equilibrium constant of the albumin-ionised calcium complexes, with acidosis reducing the binding and alkalosis enhancing it. When major changes in serum proteins or pH are suspected, measurement of ionised calcium is recommended to determine the physiological serum calcium level.

What is the prevalence of hypercalcaemia?

Primary hyperparathyroidism is a relatively common endocrine disorder, with an estimated prevalence of 1-7 cases per 1000 adults.[4 5] It is considered the most common cause of hypercalcaemia, predominantly affecting the older population (≥65 years) and women two or three times more frequently than men.[4 5] The incidence of primary hyperparathyroidism is poorly defined; evidence from the United Kingdom[5] and the United States[6] shows a wide range, from 0.41 to 21.6 cases per 100 000 population annually. This variety arises from heterogeneity in screening methods, case definition, and population studied, as well as unexplained annual fluctuations in incidence within the same population.[7]

Data on the prevalence and incidence of hypercalcaemia from other causes are poor. Malignancy associated hypercalcaemia is estimated to affect 2.7% of people with cancer in the USA.[8] Data in children with cancer indicates a lower frequency of hypercalcaemia (about 0.5-1%).[9]

What causes hypercalcaemia?

The box summarises the most common causes of hypercalcaemia. Mechanisms associated with hypercalcaemia are classically divided into parathyroid hormone and non-parathyroid hormone mediated.

Parathyroid hormone mediated hypercalcaemia

Parathyroid related causes of hypercalcaemia comprise primary (including the various genetic forms) and tertiary hyperparathyroidism. Parathyroid hormone is the main regulator of calcium homeostasis and its primary increased secretion alters the regulation of serum calcium by acting on different target organs (bone, kidney, gut).

A particular genetic form is represented by familial benign hypocalciuric hypercalcaemia. This disorder results from altered calcium sensing receptor function and a decreased sensitivity to increases in extracellular calcium; the latter determines an impaired suppression of parathyroid hormone secretion by the

Correspondence to: S Minisola salvatore.minisola@uniroma1.it

The bottom line

- Primary hyperparathyroidism and malignancy are the two most common causes of increased serum calcium levels
- The diagnosis of hypercalcaemia is made when the corrected serum calcium concentration is 2 standard deviations above the mean of values found in people with normal calcium levels, in at least two samples at least one week apart over a period of three months
- The presence of high or not adequately suppressed serum parathyroid hormone levels should point the diagnosis towards hypercalcaemia of parathyroid origins
- Mild hypercalcaemia is usually caused by primary hyperparathyroidism, the treatment for which is typically surgery; those aged 50 or more with serum calcium levels <0.25 mmol/L above the upper limit of normal and without end organ damage may be followed up conservatively. Treatment with a calcimimetic agent, cinacalcet, is an option in selected cases
- Severe hypercalcaemia requires admission to hospital and treatment with aggressive intravenous hydration and bisphosphonates along with treatment of the underlying disease

Sources and selection criteria

We carried out a search through Medline and PubMed of articles published from 1990 to 2015 using the terms “mild hypercalcaemia” and “severe “hypercalcemia”, “primary hyperparathyroidism”, “hypercalcemia of malignancy”, “parathyroid hormone measurement”, “parathyroidectomy”, and “cinacalcet” and through the National Cancer Institute using the term “hypercalcaemia”. We also retrieved personal archived references to identify peer reviewed articles. We gave priority to randomised controlled trials, systematic reviews, meta-analyses, and prospective epidemiological studies. As appropriate we also included observational, retrospective, and non-randomised studies and case reports.

Box Common causes of hypercalcaemia. Adapted from Minisola et al[26]

Parathyroid hormone mediated

- Sporadic (adenoma, hyperplasia, or carcinoma)
- Familial (multiple endocrine neoplasia 1, 2a, or 4, hyperparathyroidism jaw tumour syndrome, familial isolated hyperparathyroidism, familial hypocalciuria hypercalcaemia)
- Ectopic parathyroid hormone in malignancy (rare)
- “Tertiary” hyperparathyroidism

Malignancy

- Humoral hypercalcaemia of malignancy (parathyroid hormone related protein)
- Local osteolysis (cytokines, chemokines, parathyroid hormone related protein)
- Ectopic parathyroid hormone in malignancy (rare)
- Calcitriol related hypercalcaemia

Vitamin D related

- Granulomatous disease (for example, sarcoidosis, tuberculosis, berylliosis, coccidiodomycosis, histoplasmosis, leprosy, inflammatory bowel disease, foreign body granuloma)
- Vitamin D intoxication (vitamin D supplements, metabolites, or analogues)

Endocrine disorders

- Thyrotoxicosis
- Adrenal insufficiency
- Pheochromocytoma
- VIPoma (Verner-Morrison) syndrome

Drugs

- Thiazide diuretics
- Lithium
- Milk-alkali syndrome (calcium and antacids)
- Vitamin A
- Parathyroid hormone

Other

- Coexisting malignancy and primary hyperparathyroidism
- Immobilisation
- Acute renal failure
- Chronic renal failure treated with calcium and calcitriol or vitamin D analogues
- Renal transplant

parathyroid cells and continuous reabsorption of calcium by the kidney tubules. As a consequence, such people develop hypocalciuria, with tubular calcium reabsorption being increased by parathyroid hormone as well.

Lithium induced hypercalcaemia could be considered as a reversible form of parathyroid hormone mediated hypercalcaemia. Lithium can directly stimulate parathyroid hormone secretion and increase renal calcium reabsorption; these effects may be reversed by withdrawal of the drug.

Non-parathyroid hormone mediated hypercalcaemia

Hypercalcaemia of non-parathyroid origin is mostly related to production of parathyroid hormone related protein, calcitriol, or cytokines as mediators (box).

Malignancy related hypercalcaemia—humoral hypercalcaemia of malignancy is a paraneoplastic syndrome resulting from the secretion of parathyroid hormone related protein by the tumour.[10] Although any kind of neoplasia may cause the syndrome of humoral hypercalcaemia of malignancy, squamous carcinomas are most commonly implicated. Hypercalcaemia may be due to local osteolysis, most usually observed in haematological cancers. Overproduction of calcitriol represents the key mechanism in the development of hypercalcaemia associated with some forms of malignancy and with granulomatous diseases (box). Malignant cells and granulomas can over-express 1-α-hydroxylase and increase the conversion of calcidiol to the active form of vitamin D, calcitriol, leading to increased intestinal absorption of calcium, hypercalciuria, and hypercalcaemia. Finally, authentic ectopic hyperparathyroidism is a rare cause of hypercalcaemia, with few cases described in the literature.[10]

Thiazide diuretics—thiazides are commonly prescribed and can increase renal reabsorption of calcium, resulting in hypocalciuria and eventually high serum calcium levels. As many as 8% of people develop hypercalcaemia while taking thiazides.[11 12]

Endocrine disorders—hypercalcaemia is relatively common in people with hyperthyroidism and is probably related to increases in RANK-ligand mediated bone resorption, stimulated by an excess of thyroid hormones.[10] Hypercalcaemia can be sustained by primary hyperparathyroidism in patients with pheochromocytoma in the setting of multiple endocrine neoplasia type 2. Some pheochromocytomas have been found to secrete parathyroid hormone related protein or to directly stimulate bone resorption.[10] Hypercalcaemia is not a common finding in Addisonian crisis, but it could occur in association with the underlying disorder, such as tuberculosis; reduction in the extracellular fluid volume associated with the relative hyperalbuminaemia may lead to factitious hypercalcaemia.[10]

Acute renal failure and rhabdomyolysis—patients with rhabdomyolysis associated acute renal failure may develop hypercalcaemia. The hypercalcaemia is probably related to severe secondary hyperparathyroidism in the acute, oliguric phase—the effect of parathyroid hormone on bone along with the release of calcium phosphate into soft tissues during the early hypocalcaemic and hyperphosphataemic phase. The use of calcium, calcitriol, or vitamin D analogues supplementation in patients who have end stage renal disease or receive dialysis may cause hypercalcaemia; in this setting, hypercalcaemia may also occur in association with tertiary hyperparathyroidism. Finally, increased serum calcium levels may be observed after kidney transplantation.[10]

Immobilisation hypercalcaemia—this arises from suppression of bone formation and increased bone resorption, with consequent loss of calcium from the skeleton and hypercalcaemia. Immobilisation hypercalcaemia is generally observed when there is a concomitant cause of high bone turnover, such as in younger people. However, data from observational and retrospective studies suggest that hypercalcaemia may develop in cases of prolonged immobilisation from different causes, such Parkinson's disease or prolonged intensive care for major burns.[13 14]

Malignancy related hypercalcaemia

The occurrence of hypercalcaemia together with systemic symptoms (for example, fever, weight loss, decreased appetite, worsening malaise) or rapid onset hypercalcaemia, typically with very high serum calcium levels, should raise suspicion of malignancy. In particular, suppressed or undetectable serum parathyroid hormone levels are found in the setting of hypercalcaemia of malignancy. Hypercalcaemia is usually a late finding in malignancy and therefore the underlying disease is often known when it occurs. If the primary malignancy is unknown, the need for a rapid differential diagnosis is critical, as hypercalcaemia represents a negative prognostic factor in people with cancer. Physical examination (including lymph nodes, rectal, breasts, gynaecological, mouth, and ear, nose, and throat) should be performed, as well as laboratory assessment including blood count, biochemistry, serum tumour markers, chest, abdomen, and pelvis imaging. Serum and urinary immunoelectrophoresis are recommended, whereas in selected cases, measurement of serum parathyroid hormone related protein (where available)[19] and calcitriol might be of value. The finding of an increased parathyroid hormone related protein level implies the need to search for solid tumours (lung, oesophagus, skin, cervix, breast, and kidney are the most commons sites)[19] (see box). High serum calcitriol levels are typically associated with lymphoproliferative and granulomatous disorders (table). In this context, diagnoses should be considered even in the setting of normal serum calcitriol levels when parathyroid hormone and parathyroid hormone related protein levels are suppressed. The production of the active form of vitamin D is no longer subject to regulation by parathyroid hormone or parathyroid hormone related protein, but rather primarily driven in these conditions by the underlying disease.

Parathyrotoxic crisis

Although acute and severe hypercalcaemia is mostly associated with malignancy, the measurement of parathyroid hormone levels has a key role in excluding parathyrotoxic crisis, the association of which with parathyroid carcinoma has been described in case reports.[20 21] The clinical presentation is severe and patients require admission to hospital. Parathyrotoxic crisis comprises profound volume depletion, coma, heart failure, and abdominal pain possibly mimicking acute abdomen.

Hyperthyroid activity can be associated with hypercalcaemia and suppressed parathyroid hormone serum levels. Evaluation of thyroid function is therefore needed.

Mediators of hypercalcaemia are typically suppressed in immobilisation hypercalcaemia; serum phosphorus levels are often high, thus helping to differentiate those cases from primary hyperparathyroidism, where phosphorus levels are typically low.

Hypercalcaemia associated with suppressed parathyroid hormone, normal parathyroid hormone related protein, and high or normal serum calcitriol levels strongly suggest the diagnosis of calcitriol mediated diseases (box); however, other possible diagnoses should be taken into account. Levels of calcidiol should also be checked, particularly in those whose clinical presentation does not suggest the presence of malignancy. Clinical case reports suggest that the occurrence of vitamin D toxicity, although unusual, should be excluded, particularly when the consumption of high doses of exogenous vitamin D is unrecognised.[22] The misuse of high dose vitamin D preparations (daily dosing rather than weekly or monthly) should be investigated.

Thiazide diuretics

In patients who were hypercalcaemic while taking thiazide diuretics, serum calcium and parathyroid hormone levels should be re-evaluated at least three weeks after withdrawal of the drugs. In a population based study, about two third of patients who discontinued thiazides had persistence of hypercalcaemia, suggesting that primary hyperparathyroidism is common in those who develop hypercalcaemia while taking thiazides.[12]

How should hypercalcaemia be investigated in primary care?

The primary goal in the differential diagnosis of hypercalcaemia is to determine the underlying mechanism.

Medical history should focus on the use of supplements and drugs possibly causing hypercalcaemia (box) and include an evaluation of family history aimed at identifying underlying genetic forms of primary hyperparathyroidism.

Clinicians need to evaluate carefully the severity of clinical presentation, degree of hypercalcaemia, and timing of development of the condition. It is clinically relevant to distinguish those people with mild hypercalcaemia from those with a more severe form, as this could help in diagnosis and guiding further investigation. The table⇓ describes the clinical presentation of people with hypercalcaemia. Importantly, symptoms associated with chronic hypercalcaemia are related to severe forms—those with chronic mild hypercalcaemia are typically asymptomatic.

Contrary to what is observed among inpatients, hypercalcaemia is most commonly attributable to primary hyperparathyroidism in the outpatient setting. In this context the finding of pre-existing mild hypercalcaemia may suggest the diagnosis of primary hyperparathyroidism. However, the detection of mildly increased serum calcium levels on a routine biochemical panel in asymptomatic people is also a common finding.

The evaluation of "outpatients" with hypercalcaemia usually follows a stepwise diagnostic approach (figure⇓). Laboratory evaluation should first include the confirmation of hypercalcaemia by remeasuring serum calcium levels and correcting for albumin or by measuring serum ionised calcium wherever available. Renal function should also be evaluated. Second or third generation immunoradiometric parathyroid hormone assays should be used, as they have been proved to perform similarly and better than first generation assays[15 16]; with a sensitivity in diagnosis of primary hyperparathyroidism ranging from 88% to 97%. Hence, confirmation of hypercalcaemia in association with an increased or non-suppressed or normal parathyroid hormone concentration suggests primary hyperparathyroidism as the most likely diagnosis.

Assessment of vitamin D status is indicated, as low serum calcidiol (25(OH)D) levels are highly prevalent in people with primary hyperparathyroidism and have been associated with many negative outcomes in cross sectional studies.[16] Most recent guidelines suggest a cautious replenishment with supplemental doses of vitamin D in case of hypovitaminosis[17]; however, since no data from large randomised controlled trials are currently available, there is no specific recommendation on the dose regimen of vitamin D. Serum levels between 50 and 75 nmol/L are considered the goal of treatment in these patients.[17 18]

The diagnosis of primary hyperparathyroidism should be confirmed by ruling out familial hypocalciuric hypercalcaemia, another possible cause of high serum calcium associated with high or unsuppressed serum parathyroid hormone (box). A 24 hour urine collection for calcium and creatinine determination should therefore be performed to calculate the calcium to creatinine clearance ratio. As calcium excretion could possibly be decreased in association with vitamin D deficiency, the accuracy of this evaluation implies the need for replenishment in deficient patients. Calcium to creatinine clearance values less than 0.01 are strongly indicative of familial hypocalciuric hypercalcaemia and require an evaluation of family history of hypercalcaemia and eventually screening of serum calcium in family members. Serum magnesium could be helpful in pointing towards the differential diagnosis of familial hypocalciuric hypercalcaemia, as it is typically in the high range of normal or modestly increased in this condition. Genetic testing is useful for confirmation of the diagnosis.[16]

How is hypercalcaemia treated?

Understanding the mechanism of hypercalcaemia is crucial for the most efficient management. Regardless of the diagnosis, all patients with hypercalcaemia require hydration. The timing and regimens of hydration strongly depend on the severity of the hypercalcaemia.

Mild hypercalcaemia

Mild hypercalcaemia (values not exceeding 0.25 mmol/L above normal range or <3 mmol/L) is usually caused by primary hyperparathyroidism. Adults aged 50 or more with primary hyperparathyroidism, a serum calcium level less than 0.25 mmol/L above the upper limit of normal, and without end organ damage may be followed up conservatively—that is, without intervention and specific drugs. People with serum calcium levels greater than 0.25 mmol/L above the normal range, even if asymptomatic, should be referred for surgery. In addition, regardless of calcium levels, the most recent guidelines for asymptomatic people with primary hyperparathyroidism suggest a more complete evaluation of skeletal and renal complications, including imaging studies.[23 24] Skeletal (osteoporosis, as evaluated by bone mineral density measurement, fragility fractures) or renal involvement (nephrolithiasis or nephrocalcinosis, creatinine clearance <60 mL/min, or hypercalciuria >10 mmol/d associated with an increased risk of stone disease) and age less than 50 years are considered criteria for surgery in people with primary hyperparathyroidism, even when calcium levels are not greater than 0.25 mmol/L above the normal range.[23] In those who decline surgery or are not suitable candidates for surgery, serum calcium and creatinine levels should be measured every year and bone density measured every one or two years, together with monitoring by renal imaging. During follow-up, if the increase in serum calcium levels is greater than 0.25 mmol/L or there is renal or skeletal involvement the patient should be referred for surgery.[23]

If surgery is not performed, or not indicated, patients should be encouraged to have an above average intake of fluids and avoid drugs, such as thiazide diuretics, that can increase plasma calcium levels.[24]

Recently, cinacalcet, a calcimimetic agent, has been proved in a prospective observational study to be effective in lowering serum calcium levels in people with sporadic and familial primary hyperparathyroidism, but it has no effects on other features of primary hyperparathyroidism—that is, bone mineral density and hypercalciuria.[25] Cinacalcet given orally in a dosing regimen of 30-120 mg/d is generally well tolerated, with only nausea described as a common adverse event. The European Medicines Agency in 2008 and the US Food and Drug Administration in 2011 approved the use of cinacalcet in people

with primary hyperparathyroidism with specific indications. The EMA panel stated that cinacalcet can be an option in those where parathyroidectomy is indicated based on serum calcium levels but for whom surgery is otherwise "not clinically appropriate or contraindicated." The FDA approves the use of cinacalcet in primary hyperparathyroidism for people with severe hypercalcaemia who are unable to undergo parathyroidectomy.

Severe hypercalcaemia

If serum calcium levels are moderately increased (3.0-3.5 mmol/L), the type of treatment and timing for administering drugs should be guided by clinical manifestations. Admission to hospital is required for people with severe hypercalcaemia (>3.5 mmol/L); emergency treatment includes aggressive intravenous hydration with 3-4 litres of 0.9% saline daily, or 1-2 litre bolus of 0.9% saline, followed by 200-250 mL saline hourly.[25] The rationale underlying hydration is that people with hypercalcaemia are often severely dehydrated, mainly because of nephrogenic diabetes insipidus due to hypercalcaemia and reduced water intake. The latter results from anorexia, nausea, and vomiting induced by the hypercalcaemia itself as well as the causative disease, such as neoplasia. Hydration alone may be effective in slowly reducing serum calcium levels; however, most commonly it is not the only treatment and may lead to fluid overload. Caution is therefore needed to avoid excessive fluid loading in patients with cardiac and renal disease. In such patients, it is important to assess serum electrolytes and to carry out electrocardiography during treatment.

Loop diuretics, such as furosemide (frusemide), which could theoretically enhance calcium excretion, may worsen electrolyte derangements and volume depletion when administered at high doses. Thus, even in patients with volume overload, loop diuretics should be used with caution. A recent review of randomised controlled trials, prospective single group trials, systematic reviews, and meta-analyses shows limited or no evidence to support the use of loop diuretics in people with hypercalcaemia.[27]

Since the major mechanism responsible for severe hypercalcaemia is the increased bone resorption from activation of osteoclasts, bisphosphonates are the treatment of choice as they inhibit the osteoclast's' activity. Pamidronate and zoledronic acid are approved by EMA and FDA for the treatment of hypercalcaemia of malignancy, both having shown effectiveness in clinical trials.[28 29] Head to head comparison of pamidronate and zoledronic acid in two randomised controlled trials showed that zoledronic acid was superior to pamidronate in both efficacy and duration of response.[30] A single 15 minute intravenous infusion of 4 mg of zoledronic acid in 100 mL of isotonic saline, with adequate hydration, resulted in complete normalisation of serum calcium levels in less than three days in 80-100% of patients. Zoledronic acid can be readministered as necessary to control hypercalcaemia. The most common reported side effects have been transient fever, myalgias, and infusion site reaction. Zoledronic acid is contraindicated in patients with creatinine clearance values lower than 30 mL/min; in this situation, dose reduction according to creatinine clearance values could be an option. Ibandronate, a bisphosphonate with lower renal toxicity, is approved by EMA for the treatment of malignancy related hypercalcaemia.

As the administering of intravenous bisphosphonates out of hospital can be troublesome, patients with hypercalcaemia and end stage malignancy could benefit from subcutaneous clodronate when discharged from hospital. Subcutaneous clodronate has been reported to be effective, with no or minimal toxicity. This form of treatment may avoid hospital stay and overcome any possible problems related to difficult intravenous access.[31]

Although bisphosphonates are proved to be effective in the treatment of hypercalcaemia, a drug with a rapid hypocalcaemic effect, such as calcitonin, could be used when a prompt resolution is needed. Calcitonin inhibits bone resorption and also decreases renal tubular reabsorption of calcium. Its onset of action is within two hours of being administered, but the effect is short, and drug tolerance commonly develops within two days. Thus, calcitonin is used as an early treatment for severe hypercalcaemia until the onset of the hypocalcaemic effects of other drugs.[32]

A recent single harm intervention study in people with persistent hypercalcaemia of malignancy despite intravenous bisphosphonate treatment showed that denosumab (120 mg subcutaneously on days 1, 8, 15, and 29 and then every four weeks) lowered serum calcium levels in 64% of patients within 10 days.[33] Denosumab is a fully human monoclonal antibody that binds to RANK-ligand and inhibits the maturation, activation, and function of osteoclasts; it could be given even to those with a creatinine clearance of less than 30 mL/min. Further trials with denosumab are needed before it can be broadly recommended for use in people with hypercalcaemia.

Haemodialysis (as well as peritoneal dialysis) against a low or zero calcium dialysate is a treatment option in cases of treatment failure or when calcium levels are so high as to be life threatening; patients already receiving haemodialysis or with severe renal insufficiency may take advantage of this procedure.[34]

It should be borne in mind that in hypercalcaemia of malignancy treatment of the underlying malignancy will also reduce serum calcium levels. Surgical removal of the lesion is currently the only cure for severe hypercalcaemic crisis associated with parathyroid carcinoma, an extremely rare presentation requiring urgent admission to hospital.

Different treatments need to be considered in people with hypercalcaemia from other causes, such as vitamin D intoxication or granulomatous disorders. Since in these cases, the underlying cause is an increased production of calcidiol, drugs that enhance vitamin D metabolism, such as glucocorticoids, are indicated. Prednisone inhibits 1-α-hydroxylase and activates 24-hydroxylase, thus reducing hypercalcaemia; it is usually administered orally at a dose of 20-40 mg daily. The effects are observed within 24-72 hours of starting treatment.

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1 Dalemo S, Eggertsen R, Hjerpe P, et al. Long-term follow-up of patients with elevated serum calcium concentrations in Swedish primary care. *Scand J Prim Health Care* 2012;30:48-54.
2 Lindner G, Felber R, Schwarz C, et al. Hypercalcemia in the ED: prevalence, etiology, and outcome. *Am J Emerg Med* 2013;31:657-60.
3 National Cancer Institute. PDQ® Hypercalcemia. 2013. www.meb.uni-bonn.de/Cancernet/CDR0000062737.html.

Questions for future research

- What is the epidemiology of primary hyperparathyroidism and hypercalcaemia from non-parathyroid causes in different geographical areas of the world?
- What is a safe vitamin D serum level to target supplementation in patients with primary hyperparathyroidism who are deficient in vitamin D?
- Randomised controlled trials to define the role and safety of denosumab use in the treatment of severe hypercalcemia: could denosumab be a second line after bisphosphonates use or possible first line therapy?

Tips for non-specialists

- The diagnosis of hypercalcaemia is made when the corrected concentration of serum calcium is 2 standard deviations above the mean of values found in people with normal calcium levels, in at least two samples at least one week apart over a period of three months
- Measurement of serum parathyroid hormone and patient's clinical presentation should be rapidly assessed, particularly in severe hypercalcaemic states
- People presenting with a history of mild asymptomatic hypercalcaemia typically have a diagnosis of primary hyperparathyroidism and could be managed in the outpatient setting
- People with severe, new onset hypercalcaemia with symptoms require admission to hospital for intravenous treatment and diagnosis

Additional educational resources

Resources for healthcare professionals

Rosen CJ. Primer on the metabolic bone diseases and disorders of mineral metabolism, 8th ed. Wiley-Blackwell, 2013—discusses the pathophysiology and clinical concepts of hypercalcaemia

Bilezikian JP, Marcus R, Levine M, et al. Parathyroids, basic and clinical concepts. 3rd ed. Academic Press, 2014—discusses the pathophysiology, differential diagnosis, and clinical algorithm for the management of hypercalcaemia

National Cancer Institute, med News. Hypercalemia (www.meb.uni-bonn.de/Cancernet/CDR0000062737.html) (no registration required)

Resources for patients

Mayoclinic.org (www.mayoclinic.org/diseases-conditions/hypercalcemia/basics/definition/con-20031513) (no registration required)—discusses symptoms and causes of hypercalcaemia

BMJ Best Practice (http://bestpractice.bmj.com/best-practice/monograph/159/diagnosis.html)—(no registration required) provides a step by step diagnostic approach of hypercalcaemia; can be a useful resource for patients and clinicians to look at together for shared decision making

4 Potts JT Jr, Jüppner H. Disorders of the parathyroid gland and calcium homeostasis. In: Longo DL, Fauci AS, Kasper DL, Hauser S, eds. Harrison's principles of internal medicine. 18th ed. McGraw-Hill, 2012:3096-120.
5 Yu N, Donnan PT, Murphy MJ, et al. Epidemiology of primary hyperparathyroidism in Tayside, Scotland, UK. *Clin Endocrinol* 2009;71:485-93.
6 Wermers RA, Khosla S, Atkinson EJ, et al. Incidence of primary hyperparathyroidism in Rochester, Minnesota, 1993-2001: an update on the changing epidemiology of the disease. *J Bone Miner Res* 2006;21:171-7.
7 Yeh MW, Ituarte PH, Zhou HC, et al. Incidence and prevalence of primary hyperparathyroidism in a racially mixed population. *J Clin Endocrinol Metab* 2013;98:1122-9.
8 Gastanaga V, Jain R, Pirolli M, et al. Prevalence of hypercalcemia of malignancy in the United States. Projection methods using oncology electronic health records. *Eur J Cancer* 2013;49:S302-3.
9 McKay C, Furman WL. Hypercalcemia complicating childhood malignancies. *Cancer* 1993;72:256-60.
10 Horwitz MJ, Hodak SP, Stewart AF. Non-parathyroid hypercalcemia. In: Rosen CJ, ed. Primer on the metabolic bone diseases and disorders of mineral metabolism. 8th ed. Wiley-Blackwell, 2013:562-71.
11 Grieff M, Bushinsky DA. Diuretics and disorders of calcium homeostasis. *Semin Nephrol* 2011;31:535-41.
12 Wermers RA, Kearns AE, Jenkins GD, et al. Incidence and clinical spectrum of thiazide-associated hypercalcemia. *Am J Med* 2007;120:911.e9-15.
13 Kohut B, Rossat J, Raffoul W, et al. Hypercalcaemia and acute renal failure after major burns: An under-diagnosed condition. *Burns* 2010;36:360-6.
14 Sato Y, Honda Y, Iwamoto J, et al. Abnormal bone and calcium metabolism in immobilized Parkinson's disease patients. *Mov Disord* 2005;20:1598-603.
15 Carnevale V, Dionisi S, Nofroni I, et al. Potential clinical utility of a new IRMA for parathyroid hormone in postmenopausal patients with primary hyperparathyroidism. *Clin Chem* 2004;50:626-31.
16 Eastell R, Brandi ML, Costa AG, et al. Diagnosis of asymptomatic primary hyperparathyroidism: proceedings of the fourth international workshop. *J Clin Endocrinol Metab* 2014;99:3570-9.
17 Marcocci C, Bollerslev J, Khan AA, et al. Medical management of primary hyperparathyroidism: proceedings of the fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism. *J Clin Endocrinol Metab* 2014;99:3607-18.
18 Minisola S, Romagnoli E, Scillitani A, et al. Hypovitaminosis D in primary hyperparathyroidism: to treat or not to treat? That is the question. *J Endocrinol Invest* 2014;37:413-4.
19 Streeten EA, Jaimungal S. The differential diagnosis of hypercalcemia. The parathyroids. 3rd ed. Academic Press, 2014:607-16.
20 Minisola S, Romagnoli E, Scarnecchia L, et al. Parathyroid storm: immediate recognition and pathophysiological considerations. *Bone* 1993;14:703-6.
21 Dionisi S, Minisola S, Pepe J, et al. Concurrent parathyroid adenomas and carcinoma in the setting of multiple endocrine neoplasia type 1: presentation as hypercalcemic crisis. *Mayo Clin Proc* 2002;77:866-9.
22 Lowe H, Cusano NE, Binkley N, et al. Vitamin D toxicity due to a commonly available "over the counter" remedy from the Dominican Republic. *J Clin Endocrinol Metab 2011* ;96:291-5.
23 Bilezikian JP, Brandi ML, Eastell R, et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. *J Clin Endocrinol Metab* 2014;99:3561-9.
24 Silverberg SJ, Clarke BL, Peacock M, et al. Current issues in the presentation of asymptomatic primary hyperparathyroidism: proceedings of the Fourth International Workshop. *J Clin Endocrinol Metab* 2014;99:3580-94.
25 Schwarz P, Body JJ, Cap J, et al. The PRIMARA study: a prospective, descriptive, observational study to review cinacalcet use in patients with primary hyperparathyroidism in clinical practice. *Eur J Endocrinol* 2014;171:727-35.
26 Minisola S, Romagnoli E, Carnevale V, et al. Acute management of hypercalcemia. In: Bilezikian JP, Marcus R, Levine M, Marcocci, C, Silverberg SJ, Potts J, eds. Parathyroids, basic and clinical concepts. 3rd ed. Academic Press, 2014:617-29.
27 LeGrand SB, Leskuski D, Zama I. Narrative review: furosemide for hypercalcemia: an unproven yet common practice. *Ann Intern Med* 2008;149:259-63.
28 Kawada K, Minami H, Okabe K, et al. A multicenter and open label clinical trial of zoledronic acid 4 mg in patients with hypercalcemia of malignancy. *Jpn J Clin Oncol* 2005;35:28-33.
29 Purohit OP, Radstone CR, Anthony C, et al. A randomised double-blind comparison of intravenous pamidronate and clodronate in the hypercalcaemia of malignancy. *Br J Cancer* 1995;72:1289-93.
30 Major P, Lortholary A, Hon J, et al. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. *J Clin Oncol* 2001;19:558-67.
31 Roemer-Bécuwe C, Vigano A, Romano F, et al. Safety of subcutaneous clodronate and efficacy in hypercalcemia of malignancy: a novel route of administration. *J Pain Symptom Manage* 2003;26:843-8.
32 Reagan P, Pani A, Rosner MH. Approach to diagnosis and treatment of hypercalcemia in a patient with malignancy. *Am J Kidney Dis* 2014;63:141-7.
33 Hu MI, Glezerman IG, Leboulleux S, et al. Denosumab for treatment of hypercalcemia of malignancy. *J Clin Endocrinol Metab* 2014;99:3144-52.
34 Kindgen-Milles D, Kram R, Kleinekofort W, et al. Treatment of severe hypercalcemia using continuous renal replacement therapy with regionalcitrate anticoagulation. *ASAIO J* 2008;54:442-4.

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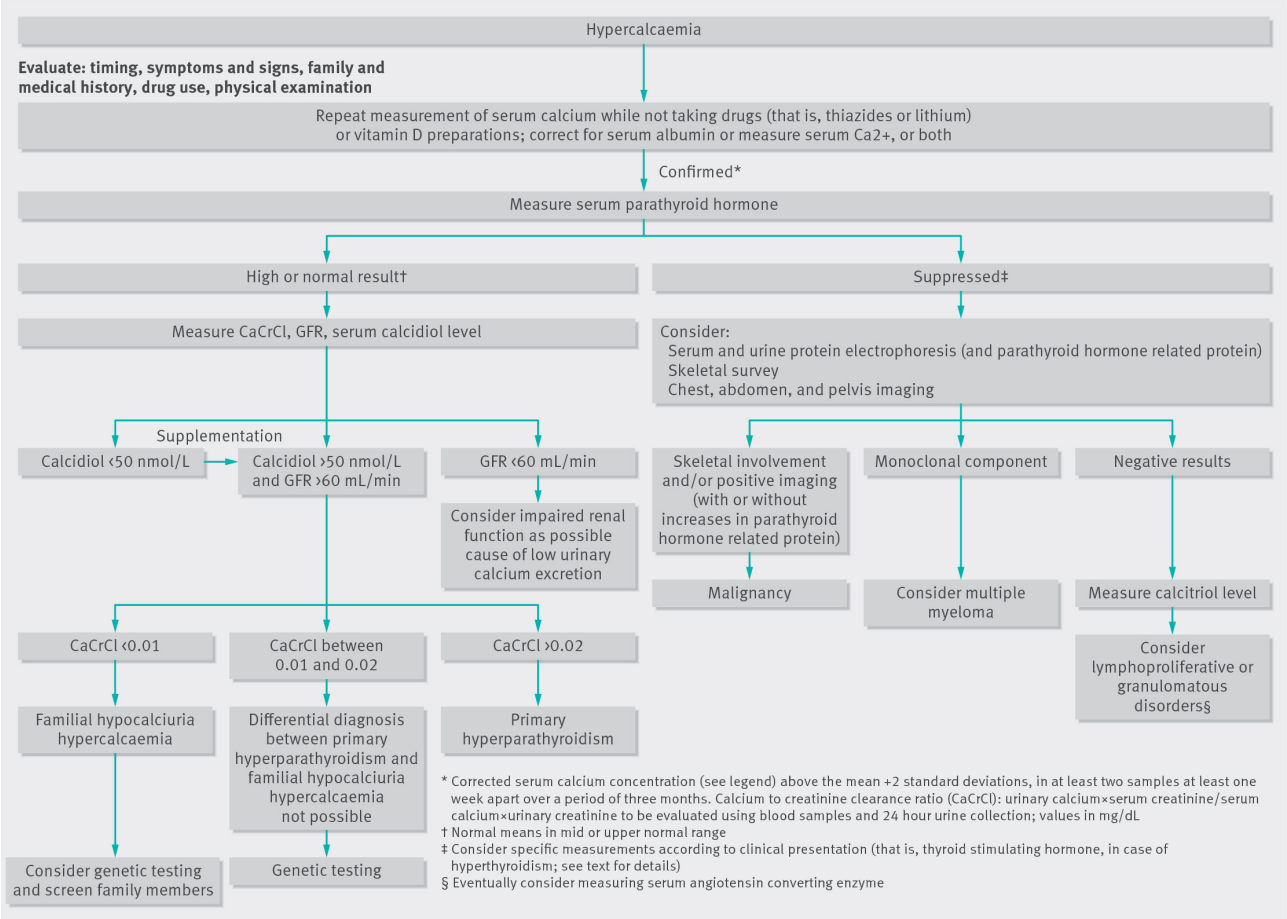
Table

Table 1| Clinical presentation of hypercalcaemia

System	Acute hypercalcaemia	Chronic hypercalcaemia
General	Flushing, fatigue, weight loss	Fatigue
Cardiovascular	Prolonged PR interval, widened QRS complex, shortened QT interval, bundle branch block, bradycardia, arrhythmias, syncope, cardiac arrest	Prolonged PR interval, widened QRS complex, shortened QT interval, bundle branch block, bradycardia, arrhythmias, hypertension, valvular heart disease, vascular calcification
Renal	Thirst, polydipsia; dehydration; polyuria; nocturia; frequent urination; renal failure from obstructive uropathy, nephrolithiasis, nephrocalcinosis, or pre-renal causes	Nephrocalcinosis, nephrolithiasis, chronic renal failure, renal osteodystrophy
Neurological	Tiredness, obtundation, lethargy, confusion, delirium, somnolence, stupor, coma, hypotonia, hyporeflexia, paresis	Dementia, memory loss, sleep disturbance, decreased concentration
Psychiatric	Irritability, depression, anxiety, hallucination, psychosis	Irritability, depression, anxiety
Gastrointestinal	Anorexia, nausea, vomiting, abdominal pain, dyspepsia, constipation, pancreatitis, peptic ulcer	Anorexia, dyspepsia, constipation, pancreatitis, peptic ulcer
Skeletal and muscle	Bone pain, muscle weakness	Bone pain, muscle weakness, myalgias, osteoporosis, osteopenia, fragility fractures, osteitis fibrosa cystica, bone cysts, brown tumours of long bones, condrocalcinosis, joint calcification
Haematological	Anaemia	Anaemia
Ocular	—	Band keratopathy (cornea)

Figure



Suggested algorithm for diagnosis of hypercalcaemia; based on available evidence, mostly derived from retrospective or observational, non-randomised, non-blinded studies. The algorithm also underlines the need for clinical evaluation as a key guide for diagnosis and management in any given patient. Corrected calcium (mmol/L)=total calcium concentration (mmol/L)+0.02(40−serum albumin concentration (g/L). Serum ionised calcium (Ca2+) should be directly measured, whenever available, through the ion specific electrode and could increase accuracy of diagnosis. GFR=glomerular filtration rate