The diagnosis and management of hypercalcaemia

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Hypercalcaemia is a common finding in the setting of primary care, as well as in emergency departments and patients admitted to hospital. Primary hyperparathyroidism and malignancy are the two most common causes of increased serum calcium levels, together accounting for about 90% of all cases. 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.

Changes in blood pH can alter the equilibrium constant of the albumin-ionised calcium complexes, with acidosis reducing the binding and alkalosis enhancing it.

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. 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.

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.

What causes hypercalcaemia?
The box summarises the most common causes of hypercalcaemia.

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

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. 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 sources and selection criteria
We carried out a search through Medline and PubMed of articles published from 1990 to 2015 using the terms “hypercalcaemia” and “malignancy.” 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.

- 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 origin.
- 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.

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.
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Hypercalcaemia

**Common causes of hypercalcaemia. Adapted from Minisola et al**

### Parathyroid hormone mediated
- Sporadic (adenoma, hyperplasia, or carcinoma)
- Familial (multiple endocrine neoplasia type 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, coccidioidomycosis, 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

Finally, increased serum calcium levels may be observed after kidney transplantation. Immobilisation hypercalcaemia — this arises from suppression of bone formation and increased bone resorption, with consequent loss of calcium from the skeleton and hypercalcaemia.

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. 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 is a negative prognostic factor. High serum calcitriol levels are typically associated with lymphoproliferative and granulomatous disorders (see table on thebmj.com). 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. 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.

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). Levels of calcitriol 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.

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.

How should hypercalcaemia be investigated in primary care?
The primary goal in the differential diagnosis of hypercalcaemia is to determine the underlying mechanism. Clinicians need to evaluate carefully the severity of clinical presentation, degree of hypercalcaemia, and timing of development of the condition. The table describes the clinical presentation of people with hypercalcaemia.
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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 immuno-radiometric parathyroid hormone assays should be used, as they have been proved to perform similarly and better than first generation assays; 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. Most recent guidelines suggest a cautious replenishment with supplemental doses of vitamin D in case of hypovitaminosis. Serum levels between 50 and 75 nmol/L are considered the goal of treatment in these patients.

The diagnosis of primary hyperparathyroidism should be confirmed by ruling out familiar 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.

How is hypercalcaemia treated?

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. 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.

Skeletally (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. 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.

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.

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 mineraldensity and hypercalciuria. 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. 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...
Suggested algorithm for diagnosis of hypercalcaemia; based on available evidence, mostly derived from retrospective or 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.

- If drinking water is calciferol-rich, consider measuring serum calcidiol level.
- Hypocalciuria is possible cause of low urinary calcium excretion.

- Measure CaCrCl§, glomerular filtration rate, serum calcidiol level.
- Consider familial hypocalciuric hypercalcaemia.
- Consider genetic testing and screening.
- Consider multiple myeloma.
- Consider lymphoproliferaitive or granulomatous disorders.

- Different treatments need to be considered in people with hypercalcaemia from other causes, such as vitamin D intoxication or granulomatous disorders.

- 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.¹²

- 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.

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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.