



Hypercalcemia Today

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Hypercalcemia is a common metabolic abnormality seen in approximately 5% of hospitalized individuals. The most common causes are malignancy and primary hyperparathyroidism. Rapid rises in serum calcium requiring urgent intervention are often due to malignancy but can also occur less commonly in association with a parathyroid crisis or other causes for the hypercalcemia (Table 1). The diagnosis of hyperparathyroidism is made in the presence of an elevated parathyroid hormone (PTH) and hypercalcemia. In patients with malignancy, the PTH level is usually suppressed.

Assessing hypercalcemia

Hypercalcemia results when there is no longer a balance between the amount of calcium entering the extracellular space from the bones or bowels and the amount of calcium being eliminated through the kidneys or deposited into bone. Serum calcium is affected by changes in renal function and the tubular handling of calcium. When hypercalcemia results in impairment of renal function due to its direct effects on the kidney or the effects of volume contraction, the serum calcium will begin to rise. This becomes a vicious cycle in which the patient can become rapidly dehydrated and experience hemodynamic instability and shock.

A history and physical examination will guide the required investigations to determine the etiology of the hypercalcemia.¹ This assessment will also help exclude a

Amy's case

Amy, 66, is post-menopausal and was found to have high calcium on routine lab testing.



- Total calcium corrected for albumin is 2.8 mmol/L
- Her parathyroid hormone (PTH) is elevated (6.8 pmol/L)
- Her 25-hydroxyvitamin D is normal (75 nmol/L)
- Her serum creatinine is normal and
- The remaining of the biochemical profile is unremarkable

Find out why Amy has hypercalcemia and how she should be investigated and treated on page 78.

Cover photograph: Blood testing (Firstlight Images®)



Table 1

Causes of hypercalcemia

1. Primary and tertiary hyperparathyroidism
2. Malignancies
 - ectopic production of 1,25 dihydroxyvitamin D
 - production of PTHrP, cytokines, growth factors, other humoral agents
 - bone metastases
3. Increased vitamin D
 - Excessive intake
 - Excessive production from granulomatous (infectious/noninfectious) diseases
4. Increased renal reabsorption of calcium
 - Familial hypocalciuric hypercalcemia (FHH)
 - Thiazide diuretics
5. Miscellaneous
 - Thyrotoxicosis
 - Pheochromocytoma
 - Adrenal insufficiency
 - Lithium
 - Vitamin A intoxication
 - Immobilization
 - Milk alkali syndrome

possible underlying malignancy that may be the cause of the hypercalcemia due to direct bone destruction or due to the release of cytokines, growth factors and possibly PTH-related peptide. This peptide can result in activation of bone resorption and the development of hypercalcemia.

Assessment will allow the evaluation of symptoms relating to the degree of hypercalcemia. Symptoms, such as polyuria, polydipsia, abdominal pain, constipation or vomiting are dependent on the rate of rise of the serum calcium. Gradual elevations of calcium are generally well-tolerated by increasing fluid intake, which enables adequate renal calcium excretion. This state of homeostasis can be affected quickly in the presence of volume contraction and the impairment of renal calcium excretion.

Inquiry into the presence of renal stones, previous fractures or episodes of pancreatitis are helpful in determining the presence of end-organ damage in primary hyperparathyroidism. Hydrochlorothiazide (HCTZ) and lithium can result in hypercalcemia. If these drugs are present, it is necessary to discontinue their use and repeat the calcium levels three months later.

The assessment of volume status is essential in the evaluation of a patient with hypercalcemia. Individuals with serum calcium > 3 mmol/L are often dehydrated and require urgent fluid resuscitation. Serum calcium should always be corrected for albumin. Approximately 50% of the calcium is bound to protein and it is necessary to correct for albumin in order to appropriately evaluate any patient with hypercalcemia, *i.e.*,

- Calcium (corrected) = Calcium + (40—albumin) X .02

Manifestations of hypercalcemia

Symptoms are dependent on the degree and the rate of hypercalcemia onset. Serum calcium as high as 3 mmol/L to 3.5 mmol/L can be well-tolerated if this develops on a gradual basis.

An acute rise in serum calcium causes acute confusion, lethargy, stupor and coma. Common symptoms of hypercalcemia include constipation (due to a decrease in the

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Hypercalcemia

tone of the smooth muscle), nausea, vomiting and anorexia.

Acute pancreatitis can occur with calcium deposition in the pancreatic duct and with activation of trypsinogen in the pancreas. Renal dysfunction occurs with a decrease in renal concentrating ability. Polyuria further contributes to volume depletion and decreases in glomerular filtration rate, further decreasing the ability of the kidney to excrete calcium. Hypercalcemia interferes with renal reabsorption of sodium and water, resulting in polyuria. Decreases in the glomerular filtration rate will further decrease renal calcium excretion and contribute to further increases in serum calcium.

Other symptoms of hypercalcemia include the presence of muscle weakness, fatigue and depression. Cardiovascular effects include hypertension, shortening of the QT interval, the development of atrioventricular blocks, bradycardia and arrhythmias (Table 2).

Hypercalcemia requires clinical assessment with exclusion of the five main causes of hypercalcemia:

- PTH-related hypercalcemia
- Malignancy
- Vitamin D-related hypercalcemia
- Drugs
- Miscellaneous

Malignancy is often clinically present when hypercalcemia occurs. It is unusual to be the presenting feature of the malignancy. Hypercalcemia in healthy outpatients is most commonly due to hyperparathyroidism. A history of longstanding polyuria and polydipsia are helpful in confirming a diagnosis of primary hyperparathyroidism, as are a history of renal stones and/or bone fractures.

Humoral factors, namely cytokines, growth factors, PTH-related protein and vitamin D, can be produced by squamous cell tumours of the lungs, head and neck, esophagus, breast, bladder and ovary. Bone metastases result in hypercalcemia with activation of the osteoclast due to the release of cytokines, such as interleukin-1 and interleukin-6. Lymphomas can produce 1,25-dihydroxy vitamin D, which can result in the development of hypercalcemia. Less common causes of hypercalcemia include vitamin D toxicity as well as granulomatous diseases, both sarcoidosis and infectious granulomatous diseases, such as TB,

Pamidronate may be given in doses of 60 mg to 90 mg and is effective in lowering serum calcium by approximately 30%.

Table 2

Clinical features of hypercalcemia

Gastrointestinal

- Nausea
- Vomiting
- Anorexia
- Constipation

Cardiac

- Arrhythmias
- Decreased QT interval

Renal

- Polyuria and dehydration
- Renal failure

Psychiatric

- Confusion
- Depression
- Psychosis
- Disorientation



Amy's followup

- Amy's PTH and calcium concentrations suggest that she may have primary hyperparathyroidism. Abdominal ultrasound should be ordered to rule out nephrolithiasis.
- Amy does show evidence of osteoporosis at the lumbar spine since her T-value at this site is -3.7 (a T-value less than -2.5 is diagnostic for osteoporosis). Her femoral neck of the hip bone mass density value shows signs of osteopenia, since it is greater than -2.5 (T = -2.1).
- You will need to repeat Amy's PTH and calcium concentrations on two more occasions in order to confirm the diagnosis. A 24-hour urine calcium and creatinine will exclude familial hypocalciuric hypercalcemia. Parathyroidectomy will correct the biochemical abnormalities and prevent further bone loss, reduce the risk of fracture and renal stones.

A history, physical, chest X-ray and lab tests will provide the correct diagnosis in 95% of patients presenting with hypercalcemia.

candidiasis and histoplasmosis. Granulomatous disease increases 1,25-dihydroxy vitamin D production and results in hypercalcemia.

Lithium can increase the set point at which calcium suppresses PTH and may appear as primary hyperparathyroidism with a slightly elevated PTH and calcium level. Similarly, hydrochlorothiazide can decrease urinary calcium excretion and normally does not increase serum calcium, but in patients with high bone turnover may do so. Vitamin D and vitamin A toxicity can both contribute to the development of hypercalcemia. Hyperthyroidism that results in hypercalcemia as T3 can stimulate the osteoclast and result in increased bone resorption.

If the PTH assay is in the upper part of the normal range in the presence of hypercalcemia, this is usually an indicator of parathyroid-dependent hypercalcemia, which may be either primary or tertiary hyperparathyroidism. Familial hypocalciuric hypercalcemia (FHH) results from an inactivating mutation of the calcium sensing receptor. This causes the calcium to be slightly high in the presence of an elevated or a high-normal PTH level. FHH should be diagnosed prior to surgery, as parathyroidectomy will not correct the hypercalcemia.

Investigation

A history, physical, chest X-ray and lab tests (including the serum immunoelectrophoresis) will provide the correct diagnosis in 95% of patients presenting with hypercalcemia. The PTH assay, checked after an overnight fast, increases the accuracy to 99%. The calcium to creatinine clearance ratio enables distinction between FHH and primary hyperparathyroidism. In FHH, the calcium to creatinine clearance ratio is less than 0.01, whereas in primary hyperparathyroidism, this ratio is greater than 0.02.

Vitamin D metabolites are helpful in excluding granulomatous conditions in which elevations in 1,25-dihydroxyvitamin D occur.

Hypercalcemia

Management

Management is urgently addressed in individuals with plasma calcium concentrations above 3 mmol/L. It is necessary to replace volume and rehydrate the patient. Approximately three to four litres of saline may be necessary within the first 24 hours, with appropriate caution given to individuals at risk for congestive heart failure. Hydrochlorothiazide should be discontinued.

Following volume repletion, loop diuretics, such as furosemide, can be given to decrease renal tubular calcium reabsorption. Calcitonin, 4 IU/kg, every six hours, subcutaneously, has a rapid onset of action and within hours is capable of lowering serum calcium.

Intravenous bisphosphonates are generally well tolerated. A small percentage of individuals may develop flu-like symptoms and a febrile reaction to intravenous (IV) bisphosphonates. IV bisphosphonates result in decreases in bone resorption. Pamidronate may be given in doses of 60 mg to 90 mg and is effective in lowering serum calcium by approximately 30% (nadir is reached by day six). Zoledronate, a more potent bisphosphonate, has a faster onset of action and can also be associated with a transient febrile reaction.

Corticosteroids are useful in managing hypercalcemia seen in individuals with granulomatous disease and malignancy. In these circumstances, corticosteroids are capable of decreasing serum calcium within several days by inhibiting the production of 1,25-dihydroxy vitamin D. Intravenous phosphate is capable of lowering serum calcium; however, this will chelate calcium and result in extra skeletal calcification. Dialysis is necessary in people with chronic renal failure and non-responders to antiresorptive therapy.

Patients who have primary hyperparathyroidism require parathyroid surgery. The guidelines for surgical intervention were recently revised by the National Institute of Health. The Canadian position paper on primary hyperparathyroidism recently reviewed the current evidence in the diagnosis and management of parathyroid disease and a multidisciplinary panel reached consensus regarding appropriate management of parathyroid disease in Canada. Current guidelines recommend surgery for those individuals with a serum calcium of

Surgical success rates, in the hands of an experienced parathyroid surgeon, are approximately 98% to 99% with a total open parathyroidectomy procedure .




Review

0.25 mmol/L or higher above the upper limits of normal. The presence of hypercalciuria with 24-hour urine calcium being more than 10 mmol/day was also an indicator for surgery, as was a reduction in creatinine clearance by 30%. The presence of osteoporosis defined at a T-score of less than -2.5 at any site of the lumbar spine, hip or radius is also a recommended indicator for parathyroidectomy, as is an age under 50 years.

Parathyroidectomy will lead to normalization of parathyroid function and plasma calcium in the vast majority of patients. Surgical success rates are approximately 98% to 99% with a total open parathyroidectomy procedure. Recently, the minimally invasive parathyroid procedure has been utilized, allowing shorter operative times and same-day discharge. It is believed that the minimally invasive procedure has a lower surgical success rate, possibly at 90%. This is currently being further evaluated.

Calcimimetic agents bind directly to the calcium sensing receptor and can result in reductions in parathyroid hormone production and secretion. The calcimimetic agent Cinacalcet was approved by the FDA in March 2004 for the treatment of hypercalcemia in patients with parathyroid carcinoma. It has been shown to be capable of decreasing serum calcium in parathyroid cancer and is a most valuable medical option for individuals with parathyroid cancer.

Hypercalcemia requires a detailed clinical evaluation with identification of the underlying cause for the hypercalcemia. Definitive therapy of hypercalcemia requires treatment of the underlying condition. Advances in the medical and surgical management of hypercalcemia enable effective diagnosis and treatment. 

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Resources

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Take-home message

- Hypercalcemia is most commonly caused by cancer or parathyroid disease.
- Patients with mild to moderate hypercalcemia are typically asymptomatic and hypercalcemia is often diagnosed on routine blood work.
- When symptoms present, they can be of gastrointestinal, renal or psychiatric manifestation.
- The first step in assessing the etiology of hypercalcemia is to determine whether the hypercalcemia is PTH dependent or not.
- General measures for correcting hypercalcemia include volume repletion, loop diuretics, such as furosemide, enabling an increase in the urinary excretion of calcium following rehydration. Antiresorptives, such as calcitonin and bisphosphonates can decrease further bone resorption. Surgery is necessary in individuals presenting with hyperparathyroidism and meeting surgical guidelines for intervention.
- Definitive treatment of hypercalcemia can only be completed once the causative mechanism is identified.