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# Diagnostic and Therapeutic Approach to Hypercalcemia: A Mini-Review and Discussion of Cases

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## Introduction

Hypercalcemia is commonly encountered in blood testing. It varies from an incidental finding in asymptomatic patients along a spectrum to more severe disease necessitating immediate emergency care and admission to a high dependency unit. If left untreated, it can lead to death secondary to cardiac arrhythmia.

The following six patients were seen at various tertiary hospitals in Australia over the last 5 years. We present their cases for discussion.

## Patient Number 1

65-year-old female admitted to the medical ward with a diagnosis of pyelonephritis.

Her past medical history included gastro oesophageal reflux disease for which she took over the counter calcium carbonate on an as needed (PRN) basis. Her vital signs were all within normal limits. Tenderness of the right costophrenic angle was present on examination. A CT scan of the abdomen demonstrated right perinephric stranding with no obstruction or hydronephrosis.

She had a series of blood tests including full blood count (FBC), C reactive protein (CRP), liver function tests (LFTs), and a metabolic panel. All blood tests were unremarkable apart from corrected serum calcium which was mildly elevated at 2.7mmol/L (1.9-2.6 mmol/L). Parathyroid hormone (PTH) was checked, and it was also mildly elevated at 53 pg/ml (11-51 pg/ml). This patient was treated with IV ampicillin as well as IV normal saline. Though she improved clinically, her serum calcium remained elevated after 3 liters of IV saline. How would you further investigate this patient's hypercalcemia?

## Patient Number 2

67-year-old female admitted to the medical ward with a cough and low-grade fever.

Her past medical history included chronic obstructive pulmonary disease (COPD) for which she used inhaled salbutamol PRN. She also had a 40 pack-year history of ongoing cigarette smoking. Her family history was significant for malignancy with both her mother and father dying of ovarian and pancreatic cancers, respectively. The patient's vital signs were within normal limits, and she did not require supplemental oxygen. Clinical examination was significant for globally reduced air entry throughout all lung fields and widespread expiratory wheezes.

A series of blood tests including FBC, venous blood gas, CRP, LFTs, and a metabolic panel were unremarkable except for CRP which was elevated at 40mg/L (0-10mg/L) and serum calcium which was elevated at 2.9mmol/L. Serum phosphate and PTH levels were checked and noted to be approaching the upper limit of normal. A chest x ray excluded pneumonia but was remarkable for bilateral hilar lymphadenopathy. She was treated with oral prednisolone and salbutamol burst therapy for a presumed non-infective exacerbation of COPD. After one day of treatment, her serum calcium dropped to 2.8mmol/L.

How would you further investigate this patient's hypercalcemia?

## Patient number 3

80-year-old male admitted with confusion, polyuria, and polydipsia.

His past medical history was remarkable for 60 pack-years of ongoing cigarette smoking. On clinical examination, he was disoriented to person, place, and situation. He was unable to follow one-step commands. There were no focal neurological signs on a limited examination. Auscultation of his chest revealed rales and whispered pectoriloquy over his right middle zone. An arterial blood gas demonstrated type 1 respiratory failure, and a series of blood tests was ordered including FBC, metabolic panel, CRP, and LFTs.

The patient was commenced promptly on IV ceftriaxone and azithromycin. Due to his confusion, a CT scan of the brain was ordered which did not show any acute pathology. While in the Emergency Department (ED), he became unresponsive and pulseless, and cardiac monitoring revealed sustained ventricular tachycardia. A code blue was called, and the patient was resuscitated for 40 minutes, with no success. After his death, his initial blood tests were reported, and the serum calcium was elevated at 5mmol/L. Was this death avoidable? Should his care have been handled differently?

## Patient Number 4

50-year-old male admitted with chest pain at rest.

His past medical history was unremarkable apart from 20 pack-years of ongoing cigarette smoking. His ECG demonstrated normal sinus rhythm with no ischemic changes, and serial troponins were not elevated. A trans thoracic echocardiogram was unremarkable and did not display any regional wall motion abnormalities consistent with acute or previous myocardial infarction. Pulmonary function testing was unable to be performed due to pain. He was treated with regular paracetamol, morphine sulphate and naproxen with good effect. A series of blood tests including FBC, CRP, LFTs, and a metabolic panel were unremarkable aside from a serum calcium of 3 mmol/L. His PTH level was normal. How would you investigate and treat his hypercalcemia? How could hypercalcemia contribute to his chest pain?

## Patient number 5

56-year-old female presented to the ED with constipation and abdominal pain.

Her past medical history was significant for bipolar disorder and hypertension. She was seen by her GP (General Practitioner) one week earlier. A thiazide diuretic was introduced due to uncontrolled hypertension, and her regular lithium was increased to 1 gram daily in consultation with her psychiatrist. An abdominal x ray demonstrated massive fecal loading. She was treated with oral gastrografin with good effect. Routine blood tests done at the time revealed a serum calcium of 3 mmol/L. How would you further investigate and manage this patient's hypercalcemia?

## Patient Number 6

22-year-old male student presented to the ED with anorexia, nausea, tremor, and anxiety. He reported an inability to concentrate when studying. Clinical examination showed tachycardia of 120 bpm, postural tremor, lid lag, fingernail clubbing in both hands, and pretibial myxedema. Results of blood testing were consistent with primary hyperthyroidism. Serum calcium was 3mmol/L. How would you further investigate and manage this patient's hypercalcemia?

## Hypercalcemia

Hypercalcemia is defined as a serum calcium level greater than two standard deviations above normal. Up to 50% of serum calcium is bound to serum albumin; therefore, calcium should first be corrected for abnormal serum albumin. Serum albumin can be low in patients with malnutrition, malabsorption, nephrotic syndrome, or a protein losing enteropathy. Low albumin can also be seen in chronic diseases, as it is a negative acute phase reactant [1]. Corrected calcium is calculated as total serum calcium (mmol/L) + 0.02 (40 – albumin [g/L]) [2]. Symptoms of hypercalcemia may include nausea, vomiting, abdominal pain, constipation, and confusion, altered level of consciousness, polyuria, polydipsia, myalgias, bone pain, and seizures. These are dependent on the level of serum calcium as well as the rapidity of its rise. If untreated, hypercalcemia can result in coma, cardiac arrhythmias, and cardiac arrest [3]. The most common causes of hypercalcemia are primary hyperparathyroidism (PHPT) and malignancy.

PHPT is a disorder characterized by overproduction of parathyroid hormone (PTH). It is typically caused by PTH secretion from benign parathyroid adenomas but can also be caused by hyperplasia of the glands themselves, or less commonly parathyroid carcinoma [4]. If PTH is detectable in the presence of hypercalcemia, the cause of hypercalcemia is most likely PHPT, though tertiary hyperparathyroidism secondary to chronic kidney disease must also be considered. Serum phosphate level and parathyroid imaging can be helpful in discriminating between these two disorders. Low phosphate in the presence of high calcium is PHPT until proven otherwise, whereas high serum phosphate and presence of adenomas in all parathyroid glands point toward a diagnosis of tertiary hyperparathyroidism [5].

In addition to parathyroid adenoma/hyperplasia, other parathyroid hormone-mediated causes of hypercalcemia include parathyroid carcinoma, familial hyperparathyroidism due to multiple endocrine neoplasia (types 1 and type 2), jaw tumor syndrome, and familial hypocalciuric hypercalcemia (FHH). Further endocrinological causes of hypercalcemia include hypothyroidism, hyperthyroidism, primary and secondary adrenal insufficiency, pheochromocytoma, and VIPoma. Additional rare causes of hypercalcemia include hypervitaminosis D (from excessive supplementation, thiazide diuretics, or granulomatous disease), acute or chronic renal failure, milk alkali syndrome, prolonged immobilization, and subcutaneous fat necrosis [6].

The following genes are associated with familial hypercalcemia: Calcium sensing receptor (CASR) in FHH, MEN1 in multiple endocrine neoplasia type 1, RET in multiple endocrine neoplasia type 2, CDKN1B in multiple endocrine neoplasia type 4, CDKN2B, CKDN2C, and CDC73 [7,8].

The 24-hour urine calcium to creatinine excretion ratio can be helpful in supporting the diagnosis of FHH in young, asymptomatic patients with a family history of hypercalcemia. This ratio will be more than 0.01 in PHPT and less than 0.01 in FHH [8]. PHPT needs follow-up and monitoring of kidney function and bone mineral density to decide on timing of surgical intervention. FHH rarely causes symptoms and does not need follow up, though genetic testing for mutations in CASR should be offered [8]. Other investigations for hypercalcemia include 25 hydroxy vitamin D and 1-25 hydroxy vitamin D to exclude granuloma, along with a technetium parathyroid sestamibi scan or single photon emission computerized tomography (SPECT) scan (if available) to assess for the presence of adenomas [9]. If parathyroid adenomas are well-localized in the setting of symptomatic PHPT, parathyroidectomy can be performed with minimal neck dissection as a day procedure [10]. Malignancy related hypercalcemia has a poor prognosis and usually causes severe symptoms; therefore, it is important to rule out this diagnosis once PHPT and FHH have been excluded. Unlike these other clinical entities, PTH is usually suppressed in hypercalcemia of malignancy [11].

Humoral and osteolytic processes are the major drivers of malignancy associated hypercalcemia [11]. Malignant hypercalcemia is most commonly due to secretion of parathyroid hormone-related protein (PTHrP) by solid organ tumors [12]. This occurs by PTHrP acting as an endocrine hormone promoting calcium resorption from bone, along with renal reabsorption [12]. Humoral hypercalcemia secondary to PTHrP is common in non-small cell cancer, urothelial cancer, and squamous cell carcinomas of the head and neck [11].

Osteolytic metastasis can also cause malignant hypercalcemia. The types of cancers most often implicated in osteolytic hypercalcemia are multiple myeloma and breast carcinoma, along with other primary cancers which have metastasized to bone [13]. Malignant hypercalcemia is rarely seen in tumor lysis syndrome resulting from initiation of cytotoxic therapy or spontaneously in highly proliferative tumors because of calcium release occurring during cellular breakdown. More commonly, however, hypocalcemia is reported in this setting as a consequence of hyperphosphatemia [14]. Rarely, lymphomas and ovarian tumors can cause hypercalcemia independent of a PTHrP- related pathway by upregulating the enzyme 1-25 hydroxylase which enhances calcium absorption from the intestines [15]. Hypercalcemia can also result from increased osteoclastic activity due to withdrawal of denosumab, the anti-receptor activator of nuclear factor kB ligand (RANKL) antibody used for treatment of osteoporosis or metastasis [16].

## Treatment of Hypercalcemia

The treatment of hypercalcemia depends on the corrected or ionized calcium level along with the acuity of its rise.

In general, asymptomatic patients with a corrected serum calcium level less than 3 mmol/L do not require urgent treatment specifically aimed at reversing hypercalcemia. Rather, the approach to this cohort of patients should focus on identifying and correcting potentially reversible causes (e.g., dehydration, use of thiazide diuretics, excess supplemental calcium, etc.). In situations where the serum corrected calcium level is greater than 3mmol/L, especially when the rise has been acute and/or a patient is symptomatic, treatment aimed specifically at reversing hypercalcemia is indicated. This should be managed in an inpatient setting where investigations into the underlying cause of hypercalcemia can be undertaken [17].

Intravenous isotonic saline should be started immediately. If a patient does not have known cardiac or renal disease and is not manifesting any signs of fluid overload a bolus of 1 liter followed by 200 - 300ml/hour is appropriate. The patient's urine output and fluid status must be assessed frequently, and the rate of fluid administration adjusted accordingly [17]. In addition to rapid commencement of treatment with IV fluid, these patients should be given subcutaneous or intramuscular calcitonin 4-8 iu/kg. Calcitonin has a rapid onset of action but should not be used after 48 hours as tachyphylaxis will occur in this period and efficacy will rapidly wane [18]. Once IV fluids and calcitonin have been initiated, serum calcium levels should be checked after 4 hours to monitor response.

Bisphosphonates are also indicated for the treatment of moderate to severe hypercalcemia, though it is important to ensure that the Vitamin D level is replete and there is not significant renal impairment before this therapy commences. It typically takes 48-72 hours for bisphosphonates to have a significant effect; therefore, they do not have to be administered with the same urgency as IV isotonic saline and calcitonin [18]. Bisphosphonate regimens include zoledronic acid 4 mg in 50 ml saline administered intravenously over 15 minutes, or pamidronate 60-90 mg over 2 hours. The RANKL-inhibiting monoclonal antibody denosumab is an alternative to bisphosphonates in patients with renal impairment and can also be used in cases of hypercalcemia refractory to bisphosphonate therapy. Depending on the degree of renal impairment as well as the underlying cause of hypercalcemia, the dose ranges from 60-120mg sub cut. Vitamin D levels should be checked, and severe deficiencies should be treated prior to commencement of denosumab. Patients with low baseline vitamin D can become hypocalcemic following administration of denosumab [19].

Patients with high 1-25hydroxy vitamin D can benefit from steroids through inhibition of 1-alpha hydroxylase and subsequent lowering of 1-25 hydroxy vitamin D levels. Patients with severe hypercalcemia secondary to parathyroid carcinoma can benefit from the calcimimetic cinacalcet as it binds to calcium-sensing receptors in the parathyroid gland, inhibits secretion of parathyroid hormone, and increases renal calcium absorption [20,21]. Cinacalcet can also be considered for treatment of severe hypercalcemia in patients with primary hyperparathyroidism who cannot undergo surgery and those with severe renal failure [22]. Patients with severe, symptomatic, life-threatening hypercalcemia, or those who cannot tolerate aggressive hydration due to severe kidney disease can benefit from hemodialysis with a low

calcium or calcium-free dialysate. Historically, IV loop diuretics such as furosemide have been included in standard therapy for hypercalcemia. These should not be given to patients unless they have significant renal or cardiac impairment as they can result in hypokalemia, hypomagnesemia, and hypovolemia [23].

In conclusion, PHPT and malignancy account for greater than 80% of cases of hypercalcemia. Less commonly, familial hypocalciuric hypercalcemia, tertiary hyperparathyroidism, medications, vitamin A and D intoxication, and an array of endocrinological diseases such as pheochromocytoma, MEN 1, 2, and 4 syndromes, acromegaly, hyperthyroidism, hypothyroidism, and adrenal insufficiency can cause hypercalcemia.

In general, asymptomatic patients do not need treatment while awaiting investigation, particularly if the corrected serum calcium level is less than 3mmol/L and they can be followed closely as outpatients. Symptomatic patients and those with a corrected serum calcium level >3mmol/L are offered inpatient treatment while awaiting the diagnosis. Malignant hypercalcemia has a grave prognosis while primary hyperparathyroidism has a benign course and can be cured by surgery when indicated.

### Patient in Vignette 1

This patient had incidental, mild, asymptomatic hypercalcemia with a slightly elevated PTH level. She had normal renal function and phosphate levels. She was not on any medications known to cause hypercalcemia, nor was she restricting her calcium intake. She did not report any bone pain, nor had she ever experienced a low trauma fracture. The differential diagnosis, therefore, could be PHPT or FHH. On discussion of family history, she mentioned that her sister had high calcium levels but was told there was nothing to worry about.

Her 24–hour urine calcium to creatinine excretion ratio was less than 0.01. She was subsequently tested for a mutation in the calcium sensing receptor which came back positive. She was diagnosed with FHH, and her doctor provided reassurance.

FHH is an autosomal dominant disease. It is usually asymptomatic and benign and does not require any medical treatment or surgical intervention. Both FHH and PHPT can affect young patients and can run in families. Differentiation between the two diseases requires testing of the 24-hour urine calcium to creatinine excretion ratio which is low in FHH compared with the elevated level seen in primary hyperparathyroidism.

### Patient in Vignette 2

This patient's chest X ray demonstrated bilateral hilar adenopathy, and his 25 hydroxy vitamin D and 125 hydroxy vitamin D were elevated despite his hypercalcemia. His PTH was low normal. A serum ACE level was elevated, and a respiratory consult was obtained. The patient was diagnosed with sarcoidosis and started on 30 mg prednisolone tapering over 3 months with improvement in chest symptoms. After 3 months, chest X ray findings, serum calcium and 1-25 hydroxy vitamin D levels had all normalized. Granulomatous disease can cause hypercalcemia through activation of extra renal 1-a hydroxylase which promotes the transformation of 25 hydroxy vitamin D to 1-25 hydroxy vitamin D.

### Patient in Vignette 3

This patient had life threatening hypercalcemia causing neurological complication in the form of confusion and decreased level of consciousness. It is difficult to say if the death was avoidable or not, as the responding MET call team was unaware that hypercalcemia was the cause of his resistant VT. A postmortem investigation confirmed non-small cell lung carcinoma (NSCLC) which was presumed to be the cause of the patient's severe hypercalcemia. Saved blood was tested for parathyroid hormone related protein, which was markedly elevated. No bone metastases were identified at autopsy. The cause of death was confirmed as ventricular arrhythmia secondary to severe humoral hypercalcemia secondary to NSCLC.

### Patient in Vignette 4

This patient had high corrected serum calcium and inappropriately normal parathyroid hormone. Additionally, he was found to have low serum phosphate, high urine calcium, and normal 25 and 1-25 hydroxy vitamin D.

All investigations for cardiac causes of chest pain were negative. A chest X ray revealed two lytic lesions in the 6th right rib. One of these lesions was biopsied, and histology confirmed osteitis fibrosa cystica. A whole-body CT-PET scan showed avid FDG uptake in the lower lobe of the right parathyroid gland. Subsequently, a technetium sestamibi scan with SPECT was performed and confirmed uptake in the right inferior parathyroid gland. This patient was treated with subtotal parathyroidectomy and subsequently developed hypocalcemia due to hungry bone syndrome. This was treated to resolution with calcium and calcitriol. His chest pain also resolved.

He was reviewed in the clinic after 6 weeks. His calcium, phosphate, and PTH all normalized with no recurrence of chest pain. A repeat X ray of the ribs demonstrated resolution of the lytic lesions. Of note, osteitis fibrosa cystica usually manifests in long bones, though fingers, facial bones, ribs, and pelvis can also be affected.

### Patient in Vignette 5

This patient presented with symptomatic hypercalcemia. Blood tests revealed an elevated serum PTH along with elevated 1-25 hydroxy vitamin D, and 25 hydroxy vitamin D levels presumed secondary to thiazide and lithium. The patient was treated conservatively with fluids, cessation of these medications, and initiation of alternative medications. On subsequent clinical review, the patient's symptoms and hypercalcemia completely resolved.

### Patient in Vignette 6

This patient had signs and symptoms consistent with Graves'

disease in the form of clubbing and pretibial myxedema. Blood testing confirmed Graves' disease with high T4, low TSH, and elevated TSH receptor antibodies. A nuclear scan of the thyroid showed diffuse uptake and increased vascularity. Along with the elevated calcium, PTH level was low, PTHrP in the upper limit of normal, 1-25 hydroxy vitamin D was elevated, and antithyroid globulin was elevated. The patient was treated with radioactive iodine with resolution of all symptoms and normalization of her serum calcium level. One year later she started to gain weight and feel cold, and blood testing confirmed hypothyroidism for which she started on thyroxine replacement.

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