Approach to the Patient with Hypercalcemia:
Diagnostic Principles

This department covers selected points from the 2008 Endocrine Update: A CME Day from the Division of Endocrinology and Metabolism at McMaster University and the University of Western Ontario.
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Hypercalcemia is commonly caused by primary hyperparathyroidism (PHPT) or malignancy.[1] These two conditions result in hypercalcemia in approximately 90% of the cases. Other less common causes include drugs, granulomatous diseases, benign tumours, hyperthyroidism and adrenal insufficiency. PHPT is a relatively common disorder with an incidence of 1 in 500 to 1,000.[2] Approximately 20% to 30% of cancer patients will have hypercalcemia at some point during the course of their illness.[3] An understanding of the physiology of calcium homeostasis and the pathophysiology of hypercalcemia, provides the physician with the ability to identify the underlying cause of hypercalcemia.

Karen's Case

Karen is a 57-year-old woman referred for assessment of hypercalcemia.

She has had stable, mild hypercalcemia over the past year.

She has not had any fractures or kidney stones, is not experiencing polydipsia, polyuria or any musculoskeletal symptoms. She has lost 10 pounds in the past 3 months, then developed loose bowel movements and heat intolerance.

Which investigations would you order?
Which conditions are important to exclude?

Read on for the answers to Karen's case.

Calcium homeostasis

Serum calcium levels are maintained in a narrow physiologic range (Table 1) by an intricate system of hormonally-mediated homeostatic mechanisms. Three hormones regulate serum calcium, namely calcitriol (1,25-dihydroxyvitamin D), parathyroid hormone (PTH) and calcitonin.

The chief cells in the parathyroid glands secrete PTH following decreases in extracellular calcium concentration. PTH increases renal calcium reabsorption in the cortical thick ascending limb, increases bone resorption and also increases the renal hydroxylation of 25-hydroxyvitamin D, thus enhancing intestinal calcium absorption. Through these actions, PTH helps to maintain serum calcium in the narrow normal range.[2,4]

Hypercalcemia

Calcium can be present in its free form (ionized) which is physiologically active, or bound to proteins largely albumin or complexed to anions such as carbonate, phosphate or sulfate. Hypercalcemia is defined as a serum calcium which is > 2 standard deviations above the normal mean value. The reference ranges may differ slightly amongst different labs.

Table 1

Normal calcium ranges

Total calcium*	Ionized calcium
2.20-2.60 mmol/L	1.15-1.30 mmol/L

*Calcium should always be corrected for albumin:
Ca(corrected)=[calcium measured]+[40-albumin] x .02.

Karen's Case cont'd...

Repeat blood work shows persistent hypercalcemia with elevated total and ionized calcium.

Parathyroid hormone (PTH) is suppressed and 1,25-dihydroxyvitamin D is normal.

Extensive investigations completed to rule out malignancy (chest x-ray, abdominal ultrasound and bone scan, serum immunoelectrophoresis) are all normal.

TSH is suppressed with elevated free T3 and free T4.

Turn to page 58 for Karen's diagnosis.

Mild hypercalcemia (2.6 mmol/L to 2.9 mmol/L) can be asymptomatic. In general, symptoms and effects of hypercalcemia are dependent on the degree of hypercalcemia as well as the rate of rise of serum calcium—thus, individuals with mild chronically elevated serum calcium can be relatively asymptomatic.[3] Renal effects include nephrogenic diabetes insipidus manifested by polydipsia and polyuria leading to volume contraction and decreased glomerular filtration rate (GFR) leading to further rises in serum calcium as renal excretion of serum calcium is impaired. Hypercalciuria contributes to the development of nephrolithiasis, nephrocalcinosis as well as prerenal azotemia. Neurologic symptoms include decreased concentration, confusion, fatigue and muscle weakness. Common GI symptoms consist of nausea, anorexia, vomiting, abdominal pain and constipation. Rarely, peptic ulcer disease and pancreatitis develop. Hypercalcemia can cause vascular calcification and cardiac arrhythmias. Most patients who present with hypercalcemia are asymptomatic and are diagnosed by the presence of elevated serum calcium on routine blood work.

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Differential diagnosis for hypercalcemia

Etiologies of hypercalcemia include: PTH-dependent and non-PTH-dependent causes.

Hyperparathyroidism

PHPT is the most common cause of asymptomatic hypercalcemia.[2] Eighty-five per cent of sporadic PHPT result from a solitary parathyroid adenoma.[5] The remainder of cases are due to hyperplasia and, rarely (< 1%), due to parathyroid carcinoma. Familial hypocalciuric hypercalcemia (FHH) is an autosomal dominant disorder which can appear in a similar manner to PHPT. It is also characterized by hypercalcemia and PTH levels may be in the upper range of normal or elevated. In FHH, relative hypocalciuria is present due to the presence of an inactivating mutation of the calcium sensing receptor (CASR) gene. This results in an increase in the set point for serum calcium suppression of PTH secretion. As the CASR is also present in the nephron it enhances calcium reabsorption, resulting in hypocalciuria, with a calcium to creatinine clearance ratio typically < 0.01. Excluding FHH is necessary prior to confirming the presence of PHPT. Patients with FHH should not undergo parathyroid surgery and this should be excluded prior to surgery.[6]

Multiple Endocrine Neoplasia (MEN), both type 1 and type II, is inherited in an autosomal dominant

Table 2

Mechanism for hypercalcemia in malignancy

Cancer	Mechanism	Mediator	Lab findings
Sqaumous cell, renal, ovarian, endometrial, HTLV-associated lymphoma, breast	Humoral hypercalcemia of malignancy (HHM)	PTHrP*	- Low PTH - Low calcitriol - High PTHrP
Breast, multiple myeloma, lymphoma	Local osteolytic hypercalcemia	Local cytokines and PTHrP	- Low PTH - Possible high PTHrP - High alkaline-phosphatase
Lymphomas	$1,25(OH)_2D$- increased due to 1α-hydroxylase activity of malignant cells	$1,25(OH)_2$-D	- Low PTH - High calcitriol

HTLV: Human T-cell leukemia/lymphoma virus
PTHrP: Parathyroid hormone-related protein

manner as is hyperparathyroidism jaw tumour syndrome which is associated with PHPT and fibromas in the mandible or the maxilla. Family members at risk can be identified by DNA analysis of the HRPT2 gene. Tertiary hyperparathyroidism can also cause hypercalcemia.[2]

Malignancy

Eighty per cent of hypercalcemia in those with cancer is due to humoral hypercalcemia of malignancy (HHM).[3] Solid tumours release parathyroid hormone-related protein (PTHrP), leading to uncoupling of bone resorption from bone formation and release of significant amounts of calcium from the skeleton into the extracellular fluid (ECF) causing hypercalcemia. In addition, PTHrP also decreases renal calcium excretion. Both of these effects result in hypercalcemia. HHM occurs in the absence of metastatic disease and is due to the effects of PTHrP.[7] In malignancy, PTHrP exerts its effects through the same receptor as PTH, the type-1 PTH receptor, however, it uncouples bone formation and resorption unlike the effects of PTH.

Hypercalcemia in malignancy

Breast cancer, multiple myeloma, leukemia and lymphoma can cause local osteolytic hypercalcemia which accounts for approximately 20% of the total hypercalcemia cases seen in cancer. Two other rare causes of hypercalcemia in neoplastic disease, accounting for < 1% of the hypercalcemia seen in cancer, are lymphomas expressing 1α-hydroxylase enzyme enhancing the production of 1,25-dihydroxyvitamin D and ectopic production of PTH by tumours.[3] Malignant cells as well as granulomatous tissue can produce 1α-hydroxylase leading to high levels of 1,25-dihydroxyvitamin D which increase intestinal calcium absorption and causes hypercalcemia.

Vitamin D-mediated

Excessive vitamin D supplements can lead to elevated 25-hydroxyvitamin D causing increased calcium absorption from the gut. In this case, PTH levels will be suppressed.

Several other diseases can cause elevated 1,25-dihydroxyvitamin D levels including Crohn's disease and other granulomatous pathological processes such

Karen's Case cont'd...

Karen had clinical evidence of hyperthyroidism and her subsequent TSH level was suppressed with elevated free T3 and free T4.

Thyroid peroxidase antibodies were positive and thyroid uptake and scan confirmed the presence of Graves' disease.

Karen was started on methimazole and her calcium levels normalized as her hyperthyroidism began to resolve.

- Confirm hypercalcemia by repeating blood work and making sure calcium is corrected for albumin concentration (calculate or measure ionized calcium)
- Measure PTH to differentiate between malignancy and hyperparathyroidism
- If PTH is suppressed, rule out malignancy or granulomatous disease

as sarcoidosis, TB and systemic fungal infections. Activated macrophages in granulomas contain 1α-hydroxylase activity enhancing the formation of 1,25-dihydroxyvitamin D.[1]

Medications

Lithium causes hypercalcemia by increasing the set-point for PTH excretion; higher blood levels of calcium are needed to decrease PTH release.[1]

Thiazide diuretics cause hypercalcemia by increasing renal calcium reabsorption. Large amounts of calcium carbonate can cause hypercalcemia, as seen in the milk-alkali syndrome, while excessive vitamin A can also cause hypercalcemia.

Other endocrine disorders

Hyperthyroidism is the most common endocrine disorder, after hyperparathyroidism, to cause hypercalcemia. Although the precise mechanism of hypercalcemia is not fully understood, it is presumed to be due to the effects of thyroid hormone on bone turnover.[8] The hypercalcemia is usually mild.

Pheochromocytoma can cause hypercalcemia. This may be due to PHPT in those with MEN type II. Some tumours have also been found to secrete PTHrP.

Addison's disease and isolated adrenocorticotropic hormone deficiency have been seen to cause hypercalcemia, although the mechanism is not known.[1] In some of these cases, volume contraction led to increased total calcium with normal ionized calcium.

How to investigate hypercalcemia

Hypercalcemia must first be confirmed by repeating lab tests. Calcium should be corrected for albumin to ensure it is not an artifactual rise. Furthermore, any drugs that can cause hypercalcemia, including OTC supplements of calcium and vitamin D, should be stopped.

The two most common causes of hypercalcemia are PHPT and hypercalcemia associated with cancer. Therefore, the first step of diagnosis must distinguish between these two causes. This can be done by measuring PTH which will be elevated in PHPT and suppressed in almost all cases of hypercalcemia associated with cancer.

If PTH is normal or elevated, urinary calcium should be measured to distinguish those who have PHPT from those with the less common FHH.[9]

If PTH is found to be suppressed, a search for malignancy must be undertaken. Tumours associated with hypercalcemia have usually become clinically evident and patients appear ill. Investigations will easily identify the tumour.[3]

Once malignancy and hyperparathyroidism have been ruled out, investigations should target the less common causes of hypercalcemia, as directed by the patient's history and physical exam. Dx

For references, please contact **diagnosis@sta.ca**