Evaluation and Therapy of Hypercalcemia

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The best treatment available for primary hyperparathyroidism is parathyroidectomy by an experienced surgeon.

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Abstract

Hypercalcemia is a common but challenging disorder. It results from PTH-dependent or independent increased bone resorption, increased vitamin D-dependent absorption, or as a result of various drugs and substances. Outpatient hypercalcemia is most commonly caused by primary hyperparathyroidism while malignancy accounts for most inpatient disease. Treatment includes adequate hydration, intravenous bisphosphonates, and occasionally calcitonin as a temporizing measure. Treating the underlying cause, such as employing chemotherapy for malignancy or parathyroidectomy for hyperparathyroidism, is also essential.

Introduction

Hypercalcemia is challenging for clinicians because of its wide differential diagnosis, non-specific presentation, and varied therapeutics. Here we review normal calcium homeostasis as a basis to discuss the pathogenesis of hypercalcemia, then examine the clinical presentation of hypercalcemia, its diagnostic evaluation, and appropriate treatment options.

Normal Calcium Homeostasis

Calcium homeostasis is balanced - urinary excretion approximates dietary intake. Typical daily intake of calcium is about one gram with about 200 mg of this being absorbed. Intestinal calcium absorption takes place through passive low-capacity and active vitamin D-dependent transcellular transport mechanisms. Half of circulating calcium is protein or anion bound. The other half circulates freely as ionized calcium and can be sensed and regulated. After intestinal absorption, calcium is absorbed into bone or renally excreted. Parathyroid hormone (PTH), secreted by chief cells of the parathyroid gland and released in response to a fall in ionized calcium, increases differentiation of osteoblasts into osteoclasts and increases osteoclast activity leading to bone resorption and calcium release. The RANK ligand-RANK-OPG system mediates these effects. In the kidney, PTH stimulates tubular calcium reabsorption and inhibits phosphate reabsorption, leading to higher serum calcium and lower phosphorus levels. PTH also stimulates 1α-hydroxylase to convert vitamin D into its active form (1,25-dihydroxyvitamin D or $1,25(OH)_2D$), which then increases intestinal calcium absorption. This active vitamin D also enhances the renal action of PTH.

Differential Diagnosis of Hypercalcemia

The etiology of hypercalcemia is most easily discussed in terms of perturbations in normal calcium homeostasis. The predominant mechanism leading to hypercalcemia is increased bone resorption.

Primary hyperparathyroidism (pHPT) occurs in 1 in 500 to 1 in 1,000 persons and is most frequent in the sixth decade of life with a female predominance. It accounts for 50-60% of outpatient hypercalcemia[1]. Eighty percent of cases are due to a single benign adenoma and 15-20% is due to four-gland hyperplasia. Parathyroid carcinoma accounts for less than 0.5% of cases[2]. An appropriate elevation of PTH in the setting of chronic kidney disease (CKD) may occur with hypocalcemia due to deficiency of $1,25(OH)_2D$, termed secondary hyperparathyroidism. More severe and long-standing CKD can lead to autonomous production of PTH termed tertiary hyperparathyroidism with resultant hypercalcemia. This may not resolve with return of normal renal function after kidney transplantation[3].

Malignancy-associated hypercalcemia (MAH) is due to increased bone resorption and is the leading cause of inpatient hypercalcemia[1]. It occurs in 20-30% of malignancies and is associated with a poor prognosis[2]. PTH related peptide (PTHrP) plays a major role in this process, increasing osteoclast differentiation and activity. Resorption of bone releases transforming growth factor beta that acts on PTHrP receptors on tumor cells to increase PTHrP production.

MAH occurs through four mechanisms[4]. First, local osteolytic hypercalcemia accounts for 20% of MAH. It occurs with extensive skeletal metastases, as in multiple myeloma and breast cancer. Local release of cytokines, including PTHrP, leads to osteoclast differentiation. Released bone matrix components are chemotactic to tumor cells and can then increase their metastatic potential. Osteoblast function can also be depressed, as in multiple myeloma[5]. Second, systemic secretion of PTHrP can lead to hypercalcemia, referred to as humoral hypercalcemia of malignancy. Squamous carcinoma is most commonly implicated but it can also be seen in renal, bladder, ovarian, breast, and neuroendocrine tumors. Third, ectopic production of $1,25(OH)_2D$ by some lymphomas and ovarian dysgerminomas can cause hypercalcemia by increasing intestinal calcium absorption. Finally, extremely rare tumors can ectopically secrete PTH – this is reported in only about ten cases in the literature[2].

Increased bone resorption induced by thyroid hormone causes mild hypercalcemia in 15-20% of thyrotoxic patients[6]. Prolonged elevations in vitamin A, causing elevated interleukin-6 levels, can also lead to increased bone resorption. This can be seen in ingestion of greater than 50,000 international units of vitamin A daily or following use of vitamin A (cis- or all-trans retinoic acid) in certain cancer treatment regimens. Immobilization and Paget's disease of bone facilitate increased bone resorption.

Increased vitamin D-dependent intestinal absorption of calcium can also cause hypercalcemia. Excessive ingestion of vitamin D in its various forms (vitamin D, calcitriol, calcidiol, or topical calcipotriol) can elevate vitamin D levels. Hypercalcemia due to calcitriol ingestion is relatively transient (one to two days) but that due to vitamin D or calcidiol ingestion can be more severe and prolonged. Hypervitaminosis D can also be due to endogenous production of $1,25(OH)_2D$ such as occurs in granulomatous diseases, including tuberculosis, fungal infections, AIDS, sarcoidosis and Wegener's granulomatosis,[7] and occasionally without identifiable causes.

Increased calcium intake in a normal person cannot cause hypercalcemia except in the milk-alkali syndrome seen with ingestion of large amounts of milk or calcium carbonate, as in the treatment of dyspepsia or osteoporosis[8], or in the setting of parenteral administration to inpatients (especially those who are immobilized). Metabolic alkalosis and renal insufficiency occur simultaneously. Hypercalcemia can also occur with concomitant treatment of vitamin D deficiency and hyperphosphatemia with calcitriol and calcium carbonate or acetate, respectively, in CKD.

Other causes of hypercalcemia include drugs, endocrine disorders, and acute kidney injury. Chronic lithium therapy likely changes the set point for PTH secretion, leading to increased PTH and hypercalcemia. Thiazide diuretics decrease urinary calcium excretion and can lead to overt hypercalcemia in those with altered bone resorption. Other substances and drugs may also rarely cause hypercalcemia, including theophylline, aluminum, and beryllium.

Acute adrenal insufficiency may cause hypercalcemia via multiple mechanisms, including altered bone and renal physiology and volume contraction. Pheochromocytoma may increase production of PTHrP or elevate calcium by mechanisms not yet identified. Resolving acute kidney injury in the setting of rhabdomyolysis can cause hypercalcemia via mobilization of calcium previously deposited in injured muscle in addition to a degree of secondary hyperparathyroidism due to the acute kidney injury. Previous secondary hyperparathyroidism may also explain transient hypercalcemia after successful kidney transplantation.

Last in the differential is the benign, mainly asymptomatic disorder, familial hypocalciuric hypercalcemia (FHH). This is an autosomal dominant condition caused by a heterozygous loss-of-function mutation in the calcium sensing receptor in parathyroid and kidney tissue[9]. The mutation results in normal or mildly elevated PTH, hypercalcemia, hypocalciuria, and normal or moderate hypermagnesemia.

Clinical Presentation

The clinical presentation of hypercalcemia depends on the degree of calcium elevation and the rapidity of its rise. Hypercalcemia affects multiple organ systems.

Most patients with pHPT will have mild hypercalcemia (<12 mg/dL) and will be asymptomatic or have non-specific symptoms. While calcium in the range of 12-14 mg/dL may be tolerated chronically, an acute rise to this level may cause significant symptoms. By contrast, in MAH, the calcium rise is usually more rapid and reaches a higher level[1].

Patients with mild hypercalcemia, especially those with pHPT, describe cognitive dysfunction, including memory difficulties, loss of initiative, anxiety and depression – all of which improve with treatment[10]. At more severe levels of hypercalcemia and especially with a rapid rise or in elderly patients, alterations in the sensorium, including lethargy, stupor and coma can occur. The electroencephalogram may show decreased voltage.

Hypercalcemia may cause bradyarrthymias. It may shorten the QTc interval but does not increase triggered arrhythmias.[11] It may increase sensitivity to digitalis.[12] Chronic hypercalcemia can lead to calcification of heart valves, the myocardium, and coronary arteries. Hypertension and pseudogout can occur more frequently, as well as diffuse arthralgias and pathological fractures. Ostitis fibrosa cystica was historically pathognomonic but due to earlier diagnosis and milder hypercalcemia, this is now rare. Hypercalcemia also results in varying degrees of peripheral muscle weakness, more proximal than distal.

Gastrointestinal symptoms include nausea, vomiting, and constipation. Hypercalcemia causes increased gastric acid and pancreatic enzyme secretion, leading to severe and recurrent peptic ulcer disease and acute pancreatitis.

The kidney manifests hypercalcemia in many ways. Twenty percent of those with chronic hypercalcemia develop polyuria and polydipsia due to decreased concentrating ability. This nephrogenic diabetes insipidus may aggravate decreased circulating volume due to nausea and poor oral intake, which then further exacerbates hypercalcemia. Long-standing hypercalcemia can lead to nephrocalcinosis due to calcium deposition in tubular cells and their eventual atrophy and resulting fibrosis. Type 1 renal tubular acidosis infrequently occurs but when it does, the resulting hypercalcuria and hypocitraturia can promote nephrolithiasis. An acute rise in calcium to over 12 mg/dL can cause reversible acute kidney injury due to direct renal vasoconstriction and volume contraction.

While historical features can be abundant, physical findings in hypercalcemia are scant. Rarely, corneal examination will reveal band keratopathy. This appears as a horizontal band across the cornea in the exposed area between the eyelids and can be seen on slit lamp examination.

Diagnostic Evaluation

First, one must determine if the hypercalcemia is authentic. Hypercalcemia without elevated ionized calcium can occur in hyperalbuminemia, severe dehydration, or in multiple myeloma with a calcium-binding paraprotein. In hypoalbuminemia due to severe malnutrition or chronic liver disease, total serum calcium may be normal with elevated ionized calcium. Correcting serum calcium for albumin is accomplished by altering the calcium value by 0.8 mg/dL for every 1 g/dL that albumin is below 4 g/dL[12]. Acidosis increases and alkalosis decreases ionized calcium due to changes in anion-bound calcium[3].

Laboratory evaluation of confirmed hypercalcemia begins with measurement of intact PTH. Elevated PTH usually indicates a diagnosis of pHPT but modest elevations can also be due to FHH and so the next step is determination of the fractional excretion of calcium $((S_{Cr}*U_{Ca})/(S_{Ca}*U_{Cr}))$. A value less than 0.01 favors FHH. Of note, about 15-20% of patients with PHTP will have high normal PTH levels[1]. Also, high calcium and PTH can be seen with lithium use[1]. For evaluation of pHPT, neck ultrasound can reveal hypoechogenic nodule(s) consistent with a parathyroid adenoma[11].

If PTH is suppressed, other causes of hypercalcemia are considered. If malignancy is readily evident, this is the likely cause and a PTHrP measurement is not appropriate. If sarcoidosis or lymphoma is suspected, an elevated $1,25(OH)_2D$ level may be detected and a chest x-ray may be appropriate. If 25(OH)D is elevated but $1,25(OH)_2D$ is not, vitamin ingestion or topical use may be suspected.

Finally, if vitamin D studies are inconclusive, other causes should be pursued and guided by history. Thyrotoxicosis can elevate calcium and chloride and may be diagnosed by a finding of a suppressed thyroid stimulating hormone level[1]. Low serum sodium in the setting of weakness or hypotension may indicate adrenal insufficiency, which should prompt assessment of serum cortisol. Other possible laboratory tests include a vitamin A level if hypervitaminosis A is possible, SPEP and UPEP (and perhaps serum free light chain measurement in those with renal failure) if multiple myeloma is suspected, or plasma metanephrines if hypertension is present and pheochromocytoma is possible.

Treatment

The degree of hypercalcemia and its rate of rise determine treatment intensity. Most patients with primary

hyperparathyroidism have mild elevations (< 12 mg/dL) and are asymptomatic or mildly symptomatic. These patients can be treated as outpatients. They must be instructed to avoid exacerbating factors, including thiazide diuretics, lithium, volume depletion, prolonged bed rest or inactivity and a diet high in calcium (greater than 1 gram/day). Adequate oral hydration of about 3 liters a day is important to prevent nephrolithiasis[11]. In patients with moderate stable hypercalcemia (12-14 mg/dL), the same precautions can be followed, but most patients with serum calcium levels above 12 mg/dL (especially those with rapid increases or with MAH) require active treatment.

Hypercalcemia causing a deterioration in clinical status is termed hypercalcemic or parathyroid crisis[11]. If due to pHPT, urgent parathyroidectomy is indicated[11]. Possible features of hypercalcemic crisis include oliguira or anuria and azotemia, somnolence and coma, cardiac arrest, severe and recurrent peptic ulcer disease, calcifying pancreatitis, nephrocalcinosis, and recurrent nephrolithiasis.

The foundation of hypercalcemia treatment is isotonic saline hydration. This corrects the volume depletion caused by hypercalcemia-induced diabetes insipidus and concomitant nausea and vomiting. Saline infusion of three to six liters over 24-48 hours can lower calcium levels by 1-3 mg/dL. Careful monitoring is essential as fluid overload can develop, especially with underlying heart or kidney disease. In this case, saline infusion should be stopped and a loop diuretic (e.g. furosemide) given. Evidence for the traditional practice of diuretic treatment combined with saline hydration is lacking.[13] The direct calciuretic effect of furosemide is expected only at doses greater than 100 mg/hour. Therefore, loop diuretics are best reserved for volume overload after adequate hydration. Hypercalcemia can be exacerbated if diuretics are administered before adequate hydration. With aggressive hydration and furosemide-induced diuresis, hypokalemia and hypomagnesemia may develop and should be corrected. Hypophosphatemia can also occur, which can promote hypercalcemia. Enteral phosphate repletion to 2.5-3 mg/dL is preferred as parenteral administration can cause severe hypocalcemia and renal failure[4].

Intravenous bisphosphonates have revolutionized hypercalcemia treatment, especially in MAH. Bisphosphonates are nonhydrolyzable analogs of inorganic pyrophosphate and are adsorbed onto bone surface. They interfere with the ability of osteoclasts to resorb bone, inhibiting calcium release. Intravenous bisphosphonates have their maximum effect at two to four days and benefits last three to four weeks. Due to the long duration of activity of these agents, it is essential to first determine the etiology of the hypercalcemia and correct reversible causes of hypercalcemia before administering these agents. Hypocalcemia can result if these agents are administered followed by correction of a reversible cause. Due to the latency of their effect, temporizing measures may be needed, especially in those with life-threatening hypercalcemia. Salmon calcitonin given intramuscularly or subcutaneously to a maximum of 6-8 IU/kg every 6 hours may lower serum calcium within 4-6 hours. Its effects are transient (lasting 24-48 hours) due to acquired resistance.

The two FDA-approved bisphosphonates are pamidronate and zoledronic acid. Both agents are associated with a risk of developing osteonecrosis of the jaw, especially in those with multiple myeloma or metastatic bone disease. Risk is greater with higher total doses and longer therapy duration. Both agents may cause a transient flu-like illness and hypophosphatemia[2]. Zoledronic acid has been found in comparative studies to be more potent and effective, though the difference is small. Pamidronate is less expensive[14] and its hypocalcemic effect resolves sooner if a reversible cause of hypercalcemia is discovered. Standard doses are 4 mg of zoledronic acid given over 15 minutes and 60 or 90 mg of pamidronate given over two to four hours. Administration should occur over a longer period of time and possibly reduced in those with renal insufficiency. In those with pHPT, intravenous bisphosphonates are reserved for the treatment of acute severe hypercalcemia. Oral bisphosphonate use in pHPT improves bone density but does not affect serum calcium or PTH levels.

Other treatments used less frequently in the treatment of hypercalcemia include glucocorticoids, gallium nitrate, mithramycin, calcimimetics, and dialysis. Dialysis against a low to no calcium bath is a treatment of last resort but may be indicated in those with severe hypercalcemia and concomitant renal or heart failure in whom hydration is difficult. Prednisone, in doses of 20-40 mg daily, can be used for patients with granulomatous disease or lymphoma. Steroids reduce calcitriol production in the activated mononuclear cells, usually within three days[2]. Gallium nitrate is rarely used because of its frequent and severe side effects including nephrotoxicity, hypophosphatemia and anemia[3]. Like bisphosphonates, it inhibits osteoclastic bone resorption and takes several days to be effective. Mithramycin is another rarely used agent that inhibits osteoclast RNA synthesis. While its effects are rapid, it has significant side effects, including elevated transaminases, nephrotoxicity, thrombocytopenia, nausea, and extravasation reactions.

Estrogens and raloxifene have been studied in post-menopausal women with pHPT, but they improve

Table 1
Indications for Parathyroidectomy in Asymptomatic Primary Hyperparathyroidism*

- Serum calcium > 1.0 mg/dL above upper limit of normal
- Age < 50 years
- Creatinine clearance < 60 ml/min/1.73m2
- T-score on DEXA of < -2.5 at any site and/or previous fracture/fragility

* No longer included is criterion for 24 hour urinary calcium levels

bone density without changing PTH or calcium levels. Calcimimetics increase the sensitivity of the calcium-sensing receptor on parathyroid cells leading to reduced PTH secretion. Cinacalcet is currently approved for secondary hyperparathyroidism due to renal failure where it has been shown to decrease PTH levels and adverse outcomes related to hypercalcemia. In pHPT, the drug may decrease serum calcium but it is not yet approved for use in this condition[15]. Cinacalcet may be used for the medical treatment of parathyroid carcinoma or hyperparathyroidism when the hypercalcemia persists after surgery or surgery is no longer feasible due to other comorbidities. Major side effects are nausea, vomiting and headache. Lastly, the FDA recently approved denosumab, a monoclonal antibody against RANK ligand for the treatment of postmenopausal osteoporosis. Agents affecting the RANK-RANKL pathway hold potential as possible future therapies for hypercalcemia, especially in the setting of malignancy[14].

Parathyroidectomy remains the curative therapy of pHPT. Guidelines for parathyroidectomy are established (see Table 1)[16]. Referral to an experienced surgeon is essential. While preoperative localization studies are popular, they do not enhance the success rate of an experienced surgeon in a neck surgery naïve patient[17]. For patients who do not undergo parathyroidectomy, monitoring is needed with biannual serum calcium levels, yearly serum creatinine and yearly bone density at three sites[18]. It is not necessary to follow 24 hour urinary calcium excretion. Low dose vitamin D supplementation (400-800 IU/daily) is needed in those with concurrent pHPT and vitamin D insufficiency or deficiency. Recent studies have shown that clinical and laboratory features of pHPT are more severe in regions where vitamin D deficiency is endemic and vitamin D deficiency seems more prevalent in pHPT[19]. Due to the risk of hypercalcemia, repletion of vitamin D must be cautious.

Conclusion

Hypercalcemia is a disorder that occurs in all age groups and is associated with morbidity and mortality. Primary hyperparathyroidism and malignancy-associated hypercalcemia account for 80-90% of hypercalcemia. Treatment is guided by a clinical determination of the need for aggressive measures. Saline hydration is essential. Intravenous bisphosphonates have strong, durable effects but their use must be limited to appropriately diagnosed patients. The best treatment available for primary hyperparathyroidism is parathyroidectomy by an experienced surgeon. Optimal approaches to hypercalcemia are still evolving given the availability of new agents.

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Disclosure

None reported.

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