Hypercalcemia

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Hypercalcemia is a potentially life-threatening metabolic disorder which may be effectively treated once its presence is recognized and its probable cause determined. The family physician should be aware of the various clinical circumstances in which hypercalcemia occurs and the appropriate initial therapy for patients who are symptomatic at the time of diagnosis. This paper provides a clear approach to the pathogenesis, diagnosis, and management of this problem.

A disorder of multiple etiologies, hypercalcemia occurs predominantly in older adults, although infants and young adults are also affected. No age group is entirely spared. Although relatively uncommon in the usual family practice setting, hypercalcemia is almost invariably associated with a significant underlying disorder, so that its presence requires further evaluation. Conversely, hypercalcemia frequently complicates the course of previously diagnosed disorders, particularly cancer, so that knowledge of appropriate therapy is essential in these circumstances. A firm understanding of hypercalcemia and its associations will provide the family physician with the ability to detect this problem earlier and provide effective therapy when needed. This paper will outline an approach to the pathogenesis of hypercalcemia and discuss its diagnostic evaluation and proper therapy.

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Calcium Homeostasis

A brief review of calcium homeostasis and physiology, as depicted in Figure 1, is helpful in understanding the causes and treatment of hypercalcemia. As shown, calcium is maintained within narrow limits by a fine balance between absorption in the gut, excretion in the kidney, and exchange with the skeletal system. This balance is mediated through the combined action of three hormones; parathyroid hormone (parathormone or PTH), calcitonin, and activated vitamin D. Specific actions of these three hormones are listed in Table 1.

Parathormone, a polypeptide, is the principal agent responsible for maintaining the level of serum calcium and is in a negative feedback relationship with the ionized serum calcium. Thus, a fall in the ionized serum calcium promotes release of parathormone, and an increase in ionized calcium inhibits parathormone release. Parathormone acts on all three target organs. It increases calcium absorption in the gut by enhancing vitamin D activity, and shifts the balance in favor of resorption and calcium release from bones. In the kidneys, parathormone promotes increased calcium resorption, increased phosphate excretion, and decreased bicarbonate resorption.

Vitamin D in the ingested form (cholecalciferol) is metabolically inactive. It is converted to the active hormone (1,25 dihydrocholecalciferol) in two steps, one taking place in the renal tubule cells and the other in the liver. Vitamin D's primary site of action is in the gut where it may significantly increase the absorption of dietary calcium. In renal parenchymal disease, hypocalcemia is aggravated by a lack of vitamin D activation often referred to as "vitamin D resistance."

Calcitonin, produced by the parafolicular cells of the thyroid, is released in response to a rise in serum calcium. Its primary site of action is on the bone where it reduces bone resorption and calcium release. It must be noted, however, that excesses of PTH can easily overcome calcitonin action.

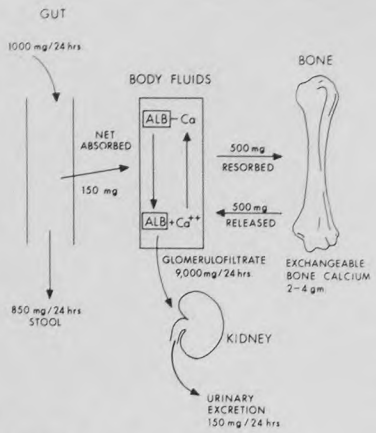

Figure 1. Calcium Homeostasis

Table 1. End Organ Effects of Regulating Hormones

Parathormone
(PTH, Parathyroid Hormone)

Gut	—	Enhances vitamin D activity; promotes calcium absorption
Bone	—	Increases osteoclastic activity and calcium release.
Kidney	—	Decreases phosphate reabsorption; increases calcium reabsorption.

Vitamin D
(Activated)

Gut	—	Increases calcium absorption.

Calcitonin

Bone	—	Reduces bone reabsorption.

Pathophysiology

Referring now to Figure 1 and Table 2, we can relate the pathogenesis of hypercalcemia to departures from the normal calcium physiology. Excessively high levels of PTH invariably result in hypercalcemia, whether the polypeptide is produced by an adenoma of one of the parathyroid glands, or by a malignant neoplasm of another organ. PTH excess results in elevated serum calcium by a combined action in the gut, the skeletal system, and in the kidneys. The previously mentioned action of PTH on the kidney results in a drop in serum bicarbonate and hyperchloremic acidosis. Thus, excess of PTH result in hypercalcemia, hypophosphatemia, and hyperchloremia. A combination of these findings can be used as evidence of hyperparathyroidism as the cause of hypercalcemia.

Excessive ingestion of vitamin D or increased sensitivity to vitamin D, as in sarcoid, may result in hypercalcemia due to increased absorption in the gastrointestinal tract. Increased intake of calcium itself, for example, the milk alkali syndrome, may also result in increased calcium absorption.

Hypercalcemia on a renal basis may be observed in patients treated with thiazide diuretics. Thiazides decrease the excretion of calcium by failing to block its reabsorption in the distal nephron.[1] This may produce mild hypercalcemia over a self-limited time. Sustained hypercalcemia with thiazides may indicate concomitant hyperparathyroidism. Transitory hypercalcemia may also occur following successful renal transplantation in patients with chronic renal failure (with previous chronic hypocalcemia and hyperphosphatemia). This latter situation is so-called "secondary" hyperparathyroidism.

The skeletal system may directly release an excess of calcium in multiple myeloma or malignant metastatic disease, presumably because of direct bony involvement. In addition, immobilization of patients with Paget's disease or occasionally of patients without underlying bone disease may lead to transient hypercalcemia.

As is the case with any disorder, there are known causes with unknown etiology. Three poorly understood causes of elevated serum calcium are: idiopathic hypercalcemia of infancy, adrenal insufficiency, and hyperthyroidism. In addition, cancers without bony metastases or PTH activity may manifest hypercalcemia, presumably due to the action of prostaglandins.

Clinical Findings

Having touched upon the various etiologies of hypercalcemia, we will now discuss the range of clinical presentations. Naturally, the first step in recognizing the signs and symptoms of hypercalcemia in any given patient is keeping in mind the set of that particular patient, ie, his/her age, sex, race, and the presence of any underlying disease. With this in mind, the presence and severity of symptoms in hypercalcemia depends on the level of serum calcium, the duration of the condition, and the underlying cause. Many patients with hypercalcemia are totally asymptomatic and are detected by means of multiphasic screening. Patients with a relatively acute onset of serum calcium elevation often present with vague, nonspecific symptoms including fatigue, muscle weakness, anorexia, and constipation. These symptoms may be easily ignored or misdiagnosed as emotional in origin. When excessive thirst, polyuria, and somnolence are the presenting symptoms, diabetes mellitus may be suspected. Patients who have long-standing hypercalcemia (such as parathyroid adenoma) usually have mild and easily missed symptoms of fatigue, muscle weakness, mood changes, and constipation. Recurrent kidney stones, dyspepsia, duodenal ulcers, hypertension, and recurring pancreatitis are also conditions associated with long-standing hypercalcemia.

Except for generalized weakness, the usual physical examination in hypercalcemia reveals very little. Calcium is deposited in the cornea in hypercalcemia and usually takes the form of a band keratopathy.[2] The calcium appears in a horizontal band beginning at the corneal margin and may be easily overlooked if not carefully looked for. Bone changes, such as simple bone cyst, subperiosteal bone resorption, and loss of lamina dura of

the teeth, are apparent on x-ray examination, but are usually clinically asymptomatic. Shortened QT intervals on the ECG require careful measurement and correlation with the heart rate. Thus, we are dealing with a syndrome which presents with a variety of common and nonspecific symptoms. It has few diagnostic physical findings and a number of related diseases which are frequently present by themselves.

Laboratory

When the presenting signs and symptoms suggest the possibility of hypercalcemia, the laboratory confirmation needs to be interpreted in light of the chemistry of calcium. One needs to account for both free (ionized) and bound calcium when interpreting total serum calcium levels. Albumin accounts for the majority of protein-bound calcium; other proteins contribute but are usually considered negligible clinically. Albumin-bound calcium and free calcium are in equilibrium, so that the decreased serum albumin which is commonly seen in cancer or other chronic systemic diseases may be associated with significant increases in ionized calcium. Ideally, in these cases a free (ionized) calcium determination would be the most direct way of evaluating hypercalcemia. However, this determination is a research tool and not generally available at this time in most laboratories, so an estimation of the effect of albumin reduction is necessary in these situations. One essential fact is that each gram of albumin is responsible for 1.8 mg% calcium. In the case of a patient with a total serum calcium of 9.0 mg% and an albumin 2 gms below normal, one should add 2 times 1.8 mg% (or 3.6 mg%) to the 9.0 mg% in order to arrive at 12.6 mg% as the "corrected" total serum calcium. This 12.6 mg% estimates what degree of hypercalcemia 9 mg% represents in conjunction with an albumin 2 gms below normal.

Table 2. Causes of Hypercalcemia

Increased PTH or PTH-like activity	Hyperparathyroidism 1° or 2°
	Ectopic PTH-producing tumor
	Tumor producing PTH-like hormone
Increased calcium intake or GI absorption	Vitamin D ingestion
	Milk alkali syndrome
	Sarcoid
Renal mechanism	Thiazide diuretics
	2° hyperparathyroidism
Skeletal destruction or increased absorption	Multiple myeloma
	Metastatic cancer
	Immobilization
Unknown etiology	Hypercalcemia of infancy
	Adrenal insufficiency
	Tumors without PTH production and/or bony metastases
	(? Prostaglandin-like substance)

Diagnostic Approach and Treatment

After a specific patient is documented to be hypercalcemic, the approach to understanding the etiology is naturally dependent upon the severity of his/her symptoms and the degree of hypercalcemia. In the case of an asymptomatic patient discovered by multiphasic screening, treatment prior to diagnosis is unnecessary. The patient should have several serum calcium determinations followed by a serum PTH level and specific inquiry into a history of renal stones, peptic ulcer disease, vitamin D ingestion, or thiazide administration. It is important to use PTH levels to differentiate between hyperparathyroidism and other causes of hypercalcemia since, in the former situation, surgical and endocrinological consultation is necessary from the onset. The diagnostic approach to increased PTH levels is to locate the PTH-producing tissue and remove it if possible. Specifics of this diagnostic approach will vary from one medical center to another. However, catheterization of the veins draining the parathyroid gland with measurement of the specific PTH level coming from a particular parathyroid gland is often used. If the clinical situation indicates carcinoma as a possible cause of increased PTH activity, then the possibility of chest x-ray tomography and bronchoscopy may be entertained. With normal or low PTH levels, the other diagnoses in Table 2 need to be considered.

When calcium levels are significantly elevated and/or the patient is

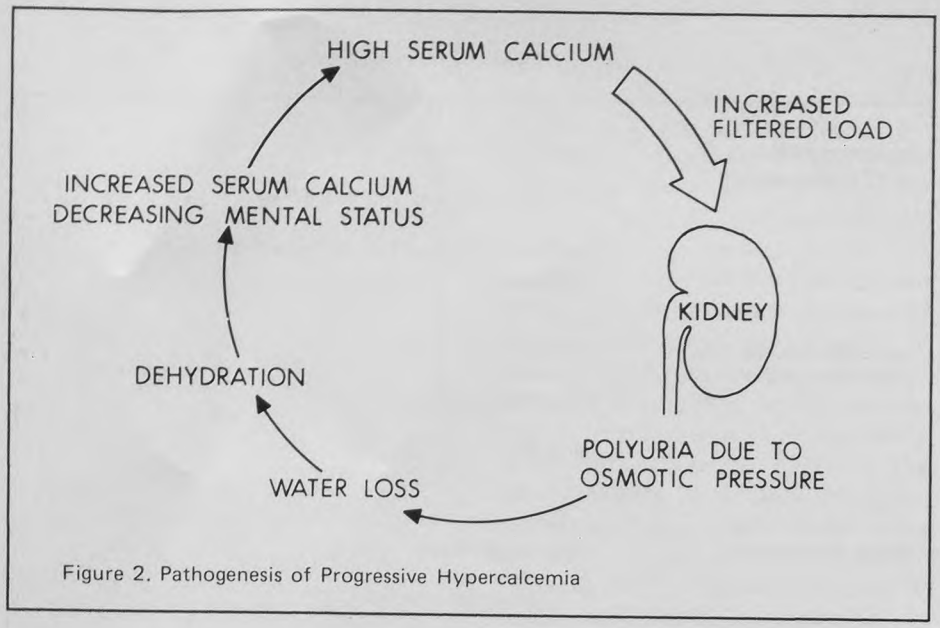

Figure 2. Pathogenesis of Progressive Hypercalcemia

symptomatic, immediate treatment may be necessary in order to prevent a possible rapid deterioration of the patient which may be fatal. Hypercalcemia which presents a high filtered load of calcium to the kidney tends to perpetuate itself (Figure 2). The calcium load promotes a diuresis and polyuria causing dehydration. Dehydration accentuates the hypercalcemia and causes anorexia and confusion. With the decreased fluid intake, continued hypercalcemia leads to further polyuria, leading to further dehydration and so forth. A vicious cycle is thus established which, if not promptly interrupted by the physician, will lead to death of the patient. As previously noted, this series of events can begin with a "near normal" serum calcium if the serum albumin is reduced. The family physician will encounter this situation most commonly in patients with cancer. Thus, particular care needs to be given to the early detection and treatment of hypercalcemia in these patients. In the symptomatic patient, the first and most important treatment is rehydration and subsequent saline diuresis once the patient is rehydrated. Since the necessary volume of saline is large, it is advisable to place a central venous catheter, and strictly monitor urine output and serum electrolytes. Once dehydration has been corrected, vigorous diuresis will usually reduce a dangerously high serum calcium dramatically. Twenty to 40 mg of furosemide (Lasix) may be administered intravenously to encourage further diuresis, provided the physician is certain that the initial dehydration has been corrected.

Once serum calcium levels have been rapidly reduced towards normal by the above emergency measures, the following therapeutic approaches can be taken in order to sustain normal or near normal calcium levels.

1. *Oral Phosphates* – Fleet's phospho-soda (5 ml three to four times a day) will bind calcium in the gut and may be used continuously if the circumstances warrant it. One side effect is diarrhea, and the medicine has a disagreeable taste. Parenteral phosphates are dangerous because of associated hyperkalemia and, therefore, are no longer used.

2. *Corticosteroids* – Steroids in large doses (hydrocortisone 250 to 500 mg every eight hours) will cause significant lowering of calcium beginning several days after administration. The mechanism of action is thought to be interference with vitamin D metabolism. Patients with hyperparathyroidism will usually not respond to steroid therapy.

3. *Mithromycin* – Mithromycin is a cytotoxic antibiotic which inhibits bone resorption and may be used in cancer patients refractory to other therapy. Given intravenously, the effect begins within hours and lasts for days to weeks. Side effects include thrombocytopenia and, thus, caution must be exercised in patients with bleeding disorders or a baseline thrombocytopenia.

4. *Calcitonin* – Calcitonin for use in treatment of hypercalcemia is available at this time under research protocol only. It promises to be a useful drug in the future for this purpose. Its mechanism of action is found in Table 1 and at the present time is certified for use only for Paget's disease of the bone.

5. *Restriction of Dietary Calcium* – Dietary restriction of calcium may also be helpful, particularly in the initial management of patients with hyperparathyroidism. In patients with cancer and anorexia due to the disease and/or hypercalcemia, however, a diet severely restricting calcium may be unpalatable and thus not practical.

Summary

Hypercalcemia is a disorder of multiple etiologies which affects all age groups. Understanding the pathogenesis of the disorder is most easily accomplished by considering alterations in the normal calcium physiology. Once hypercalcemia has been detected, a vigorous search for its etiology is essential so that appropriate therapy may be begun. The family physician should be able to detect asymptomatic patients by screening, diagnose symptomatic patients early in the disease, and initiate evaluation, consultation, and therapy for the majority of hypercalcemic patients.

References

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2. Newell FR: Ophthalmology Principles and Concepts. St. Louis, Mosby, 1969