

Assessment and management of patients with abnormal calcium

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Calcium is essential for homeostasis, and normocalcemia should be maintained strictly during the perioperative period. The biochemistry of calcium equilibrium results from the calcium-sensing receptors on the parathyroid glands, which detect changes in calcium concentrations and initiate the proper response.

Asymptomatic hypercalcemia is a common metabolic derangement that is often discovered on routine serum screening. The most common etiologies are primary hyperparathyroidism and cancer. Increasingly, parathyroidectomy is the preferred therapy for primary hyperparathyroidism. Severe hypercalcemia ("hypercalcemic crisis") should be managed aggressively with a combination of intravenous fluids, steroids, bisphosphonates, and

calcitonin. Some of these patients may require an urgent parathyroidectomy for calcium control.

Hypocalcemia needs to be verified, as many cases of hypocalcemia are the artifact of hypoalbuminemia. Severe hypocalcemia occurs after subtotal or total parathyroidectomy with auto transplantation as well as after massive resuscitation or blood transfusion. Strategies aimed at correcting calcium concentrations depend on the severity of symptomatology. If symptoms are mild, oral calcium supplementation can be given; otherwise, intravenous calcium should be administered. (Crit Care Med 2004; 32[Suppl.]:S146–S154)

KEY WORDS: calcium; hypercalcemia; hypocalcemia; parathyroid; sestamibi

Calcium is a highly regulated, ubiquitous cation that has multiple roles in the body. Since the development of life on earth, calcium has bound with organic ligands. Theoretically, calcium evolved into this role because its traits facilitate ligand interactions: It is large, positively charged, and spherical in shape (1). With evolution, calcium localized to specific areas. For example, the extracellular space is abundant with calcium, whereas the intracellular concentration remains low, except in specialized compartments such as the mitochondria and the endoplasmic, sarcoplasmic, and nuclear reticula (2). Gradients in calcium concentration are achieved through channels that regulate ion flow. The principal calcium channels are voltage-gated, ligand-gated, and second messenger-operated, and this allows cells to use calcium as the most common second messenger (3). Therefore, changes in intracellular calcium concentration affect a myriad of cell functions, including cell death or apoptosis (4); the duration and strength of cardiac muscle contraction (5); and smooth muscle contraction in blood vessels (6), airways (7), and the uterus (8). Calcium

concentration also affects platelet aggregation and function (9).

Normal Calcium Concentrations and Distribution. Calcium exists in the extracellular plasma in a free ionized state as well as bound to other molecules. "Normal" plasma concentrations of total calcium vary between laboratories, but the range of (bound and unbound) calcium is usually between 8.5 and 10.2 mg/dL (2.2–2.5 mmol/L). The biologically inert bound fraction (55% of the total) binds to proteins. Changes in albumin alter total calcium concentrations significantly, since the majority of protein-bound calcium associates with albumin (80%). A small percentage of calcium is associated with other proteins, such as β -globulins, or nonprotein molecules such as phosphate and citrate. Mathematical formulas correcting for disparate albumin concentrations (e.g., corrected calcium = decrease of 0.8 mg/dL for every 1.0 mg decrease in albumin, or $[\text{total calcium} + 0.025] \times [40 - \text{albumin}]$) can be notoriously inaccurate, and an ionized calcium concentration should be measured (10). Forty-five percent of the total calcium is biologically active and exists in the ionized form, with a normal concentration of 4.5–5.0 mg/dL (11). Ionized calcium concentrations are inversely affected by the pH of blood; an increase in pH will decrease the ionized calcium concentration by 0.36 mmol/L (12), such that pa-

tients with metabolic alkalosis often are hypocalcemic (13).

Control of Calcium Concentrations. Concentrations of calcium are highly modulated through a delicate interplay between parathyroid hormone (PTH), calcitonin, and vitamin D acting on target organs such as bone, kidney, and the gastrointestinal tract (Fig. 1). Chief cells in the parathyroid glands secrete PTH, an 84-amino acid protein, whenever calcium concentrations decrease. This, in turn, stimulates osteoclasts to increase bone resorption, the kidney to increase calcium resorption and renal production of 1,25-dihydroxyvitamin D [$1,25(\text{OH})_2\text{D}$], and the intestine to increase absorption of calcium and phosphate. Together, these processes raise the calcium concentration. The recently cloned (14) calcium-sensing receptors in the parathyroid glands detect changes in calcium concentrations, which results in a negative feedback loop that decreases PTH production.

Calcitonin is a 32-amino acid protein secreted by the parafollicular cells of the thyroid gland in response to high calcium concentrations. Its actions oppose those of PTH. Calcitonin rapidly inhibits bone resorption, leading to a transient decrease in serum calcium concentrations.

Vitamin D is ingested or synthesized in precursor form, which then undergoes two hydroxylation steps before becoming a molecule that influences calcium concentrations. The first hy-

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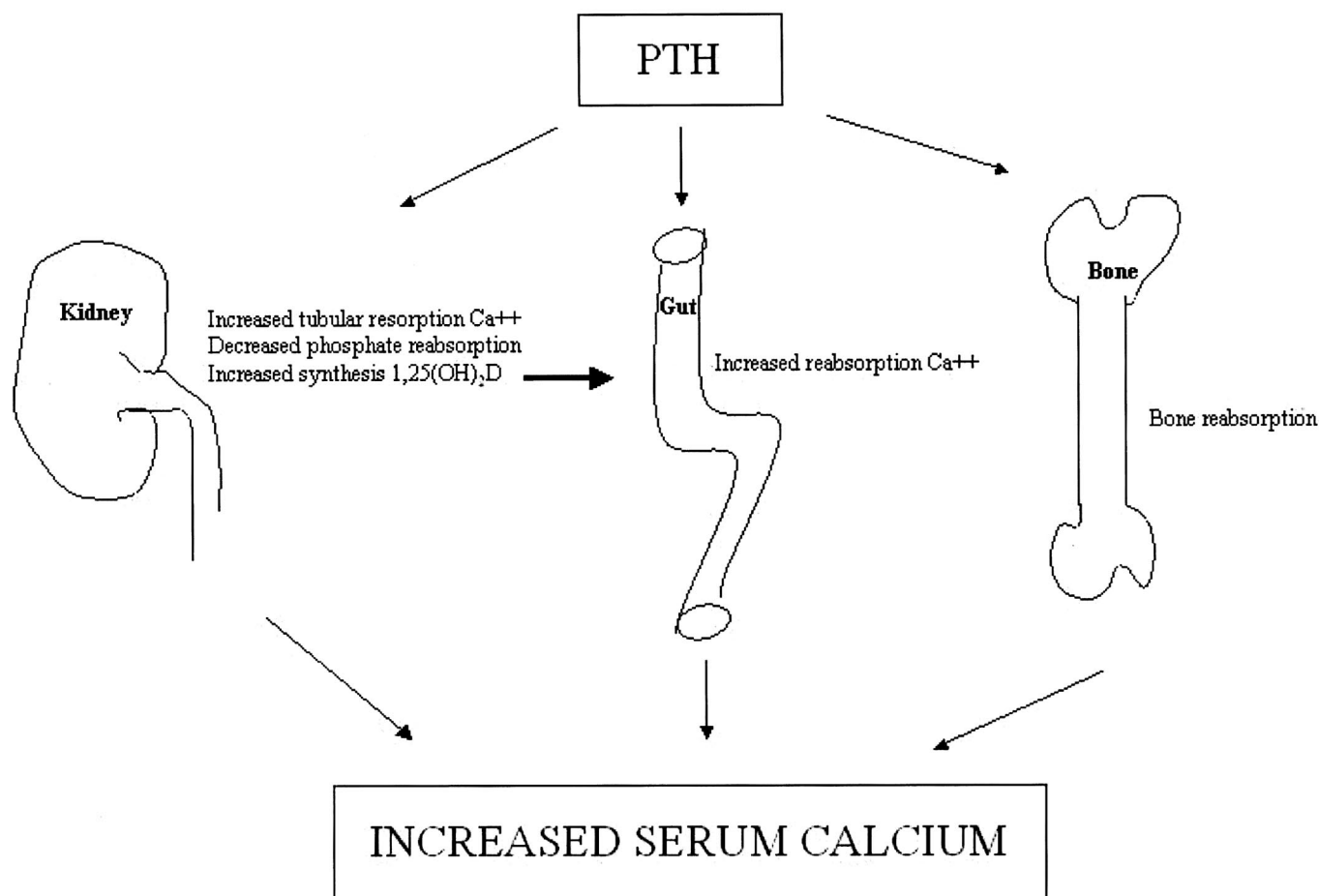


Figure 1. Calcium homeostasis and parathyroid hormone (PTH).

droxylation step at carbon 25 occurs in the liver, and the second hydroxylation step at carbon 1 occurs in the kidney in response to increased PTH concentrations. The $1,25(\text{OH})_2\text{D}$ increases calcium and phosphate resorption from the gastrointestinal tract and stimulates bone resorption, thereby raising calcium concentrations.

Preoperative Assessment: Hypercalcemia. Hypercalcemia is defined as an increase in serum calcium >1 mg/mL above the normal range (15). It affects multiple organ systems and leads to a myriad of clinical symptoms and signs. Gastrointestinal symptoms result from smooth muscle relaxation and include constipation, anorexia, nausea, and vomiting. Neurologically, patients with hypercalcemia can be lethargic, hypotonic, confused, or even comatose. Effects on the kidneys include polyuria, dehydration, and nephrolithiasis. Dehydration leads to proximal tubule resorption of sodium and calcium in an effort to expand the extracellular volume, but this

paradoxically worsens hypercalcemia (16).

Hypercalcemia also affects the electric conduction pathways of the heart. Patients with elevated calcium concentrations have electrocardiographic changes marked by shortened QTc intervals (17) (Fig. 2). Patients with hyperparathyroidism will demonstrate these electrocardiographic findings, which normalize with successful parathyroidectomy. However, cardiac arrhythmias or conduction problems generally are not associated with this phenomenon (18). In addition, severe hypercalcemia can cause the Osborn, or J wave, seen at the tail end of the QRS complex, which usually is associated with hypothermia (19).

Increased calcium concentrations also have been shown to cause pancreatitis (20, 21) (see case study presented subsequently).

Causes of Hypercalcemia

Hyperparathyroidism. Primary hyperparathyroidism is the most common

cause of hypercalcemia. The biochemical diagnosis is established by elevated serum calcium and intact parathyroid hormone (iPTH) concentrations with an inappropriately normal or increased 24-hr urine calcium concentration, all in the setting of normal renal function.

The most common cause of primary hyperparathyroidism is a parathyroid adenoma (85%). Adenomas are benign and typically affect only one gland, but in 5% of cases, two glands are affected. Parathyroid hyperplasia affects all glands and is the underlying cause of primary hyperparathyroidism in 10% of cases. It can be associated with the multiple endocrine neoplasia I and IIa syndromes. A thorough history and physical exam should be performed to exclude these autosomal dominant, multiple-organ syndromes. Multiple endocrine neoplasia I includes hyperparathyroidism, pituitary adenoma, and pancreatic tumors (most commonly insulinomas or gastrinomas). Multiple endocrine neoplasia IIa includes hyperparathyroidism, medullary carcinoma of

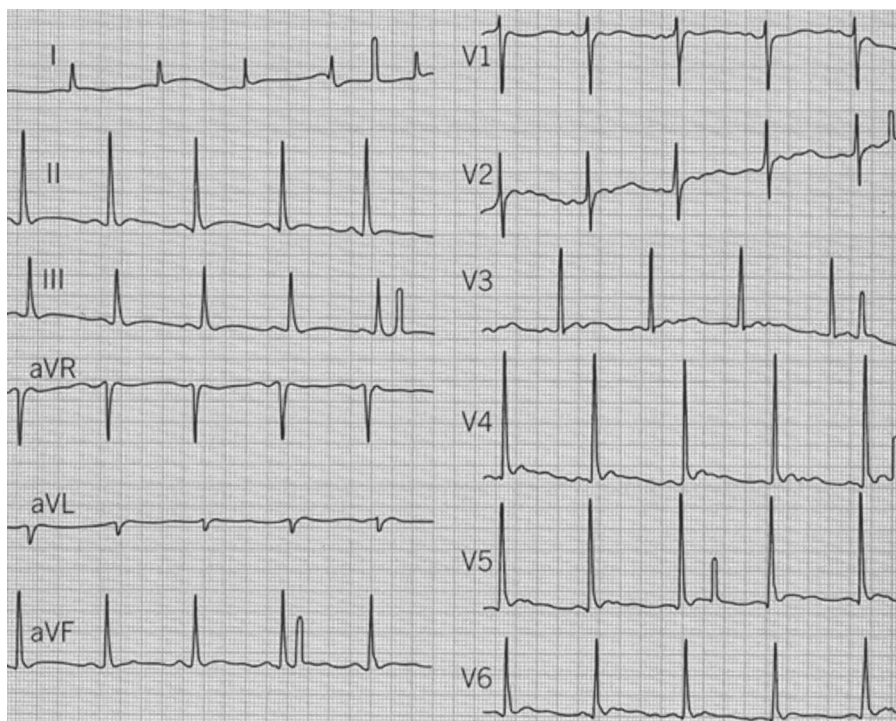


Figure 2. Electrocardiogram (EKG) consistent with hypercalcemia. The EKG demonstrates a shortened QTc interval. The QTc interval is comprised of ventricular depolarization and repolarization and is measured from the beginning of the QRS complex to the end of the t wave, corrected for heart rate. Adapted with permission from Crawford M and DiMarco J. *Cardiology* 2001; 8(4.8), New York, Mosby.

the thyroid, and pheochromocytoma. Parathyroid carcinoma is a rare (<1% of cases) cause of primary hyperparathyroidism.

Secondary hyperparathyroidism results from stimuli outside the normal feedback loop. For example, patients with renal failure have decreased renal conversion of 25-hydroxyvitamin D to 1,25(OH)₂D, resulting in less calcium absorption. In addition, these patients have hyperphosphatemia. The cumulative effect is that these patients are hypocalcemic, and PTH is secreted from the parathyroid glands. Approximately 90% of renal failure patients have secondary hyperparathyroidism; usually this can be controlled with medical management in the form of phosphate binders and vitamin D supplementation. Tertiary hyperparathyroidism occurs when the parathyroid glands of these patients become overactive and autonomous from normal negative feedback mechanisms. Patients who fail medical therapy and acquire tertiary hyperparathyroidism develop clinical sequelae such as calciphylaxis, and they should be referred for parathyroidectomy.

Benign Familial Hypocalciuric Hypercalcemia. Benign familial hypocalci-

uric hypercalcemia is an important syndrome to exclude, because patients who are heterozygous for this condition do not require surgery. The syndrome is secondary to a mutation in the calcium-sensing receptors, and it is transmitted in an autosomal dominant fashion (22). The mutation causes elevations in serum calcium, with normal or low 24-hr urinary calcium concentrations. Patients usually are asymptomatic and do not develop such clinical sequelae of hypercalcemia as nephrolithiasis or osteopenia. Homozygous patients with two defective calcium-sensing receptor genes present early in life with severe hypercalcemia and hyperparathyroidism and may benefit from a life-saving parathyroidectomy.

Hypercalcemia of Malignancy. Hypercalcemia of malignancy is secondary to the inappropriate release of PTH-related peptide (PTHrp) from tumor cells. Cloning of the PTHrp gene demonstrated that it has the same amino-terminus as the PTH gene, which allows for binding to the same receptor (23). This leads to increased bone resorption and decreased renal calcium excretion (24, 25). PTHrp is essential in the normal physiology and development of breast tissue (26, 27), placenta and smooth muscle (28), neurons

(29), and bone (30). However, inappropriate PTHrp secretion is the primary cause of the hypercalcemia of malignancy. It can lead to pathologic bone fractures and other symptoms of hypercalcemia that portend a poor prognosis (26). PTHrp-induced hypercalcemia is associated with squamous cell (e.g., lung) (31), breast, (32), prostate (33), and (rarely) colon cancer (34) as well as adult T-cell malignancies (35, 36) and multiple myeloma (37).

Granulomatous Diseases. The association between hypercalcemia and granulomatous diseases such as sarcoidosis was first documented in 1939 (38). Hypercalcemia occurs secondary to increased 1,25(OH)₂D production that is independent from the normal negative feedback mechanisms (39). Macrophages in granulomas produce 1,25(OH)₂D (40). Other granulomatous disease such as tuberculosis, leprosy, coccidioidomycosis, and histoplasmosis all have been associated with hypercalcemia via a similar pathway.

Diet and Drugs. Patients with elevated calcium concentrations should be screened to exclude dietary causes. Large amounts of supplemental calcium or vitamin D (e.g., in the form of antacids) can cause hypercalcemia. Hypercalcemia also has been reported in patients ingesting yogurt and antacids (41), betelnuts (42), and vitamin D (43). In addition, thiazide diuretics (44) and lithium (45) can cause hypercalcemia.

Preoperative Assessment: Hypocalcemia. Early symptoms of hypocalcemia include perioral numbness, paresthesias, muscle cramps, and mild mental status changes such as irritability. As hypocalcemia becomes more severe, there can be neuromuscular and cardiac findings, including Chvostek's and Trousseau's signs, as well as mental status changes, seizures, tetany, hypotension, and acute heart failure (46, 47). Chvostek's sign is elicited by tapping the facial nerve anterior to the ear, which produces spasm of the muscles of the face; it has been shown to be positive in 10–30% of people with normal calcium concentrations (48). Trousseau's sign is positive when pressure on the wrist induced by inflation of a blood pressure cuff for 3–5 mins or tapping on the median nerve induces carpal spasm.

Acute hypocalcemia decreases cardiac function by lengthening phase 2 of the cardiac action potential, which results in prolongation of the ST segment and the QT interval on electrocardiogram (Fig.

3). The effect is profound, as lengthening of the QT interval alone is an independent risk factor for arrhythmias and cardiac death (49). Patients who present to the hospital in cardiac arrest often are severely hypocalcemic (50). Hypocalcemia can lead to cardiac failure, and this can be reversed with administration of calcium (51–54). However, in patients with underlying heart disease who are also on β -blockers, hypocalcemia can precipitate more severe cardiac failure (55).

Patients with long-standing hypocalcemia may have normal cardiac function (56). Still, it is prudent to strictly keep calcium concentrations in the normal range, especially when patients have underlying heart disease. In the setting of hypocalcemia, it also is important to anticipate simultaneous abnormalities in magnesium concentrations. In this setting, intravenous magnesium administration may be necessary to achieve normalization of calcium concentrations.

Causes of Hypocalcemia

Surgery. Hypocalcemia should be avoided in the postoperative setting. Risk factors for the development of hypocalcemia after parathyroidectomy include subtotal or three and one-half gland parathyroidectomy, removal of parathyroids together with the thyroid gland, a preoperative iPTH value >25 pmol/L, or a history of a previous neck dissection (57). A recent prospective randomized trial also identified bilateral neck dissection as a risk factor compared with unilateral neck exploration (58). In addition, an intraoperative decrease in iPTH concentration of $\geq 84\%$ or low iPTH concentrations after parathyroid removal increase the risk of postoperative hypocalcemia (59, 60). Measurement of iPTH concentrations with a chemiluminescence immunometric assay (Nichols Institute Diagnostics, San Juan Capistrano, CA) has dramati-

cally changed the techniques of parathyroidectomy by allowing surgeons to perform minimally invasive, unilateral neck explorations. The assay takes <15 mins to perform, and cure can be achieved in the operating room by documenting a decrease of $\geq 50\%$ in the iPTH concentration (61, 62).

Anions. Shifts in intravascular volume seen with large resuscitations or dialysis also can cause hypocalcemia. Sudden increases in anions facilitate binding to ionized calcium (a cation), which leads to hypocalcemia. For this reason, hypocalcemia can occur when citrate is used as an anticoagulant during dialysis (63, 64), transfusions (65), or plasmapheresis (66). Phosphate also binds to calcium and can have similar effects. Use of sodium phosphate (phosphosoda) bowel prep has been associated with hypocalcemia (67–69); patients with renal failure or bowel obstruction are at particularly high risk.

Medical Conditions. Hypocalcemia is associated with pancreatitis (70), malnutrition with vitamin D deficiency, meningococcal sepsis (71), and critical illness (72, 73). In addition, there are case reports of hypocalcemia associated with labor/delivery and lactation (74).

Children can present with hypocalcemia, particularly when born prematurely or when the pregnancy is complicated by diabetes (75). There is an association between hypocalcemia in premature children and atrioventricular heart block (76).

Management of Calcium Abnormalities

Hypercalcemia. The management of hypercalcemia involves medical and surgical strategies. Mild asymptomatic hypercalcemia discovered on preoperative assessment should be evaluated further, whereas symptomatic hypercalcemia requires more urgent therapy (Fig. 4).

Pharmacologic agents associated with hypercalcemia should be discontinued; specifically, digoxin potentiates arrhythmias in the setting of hypercalcemia and should be discontinued (77).

In the setting of hypercalcemia, initial management is medical and promotes the renal excretion of calcium (78). Intravenous fluids, preferably normal saline, are administered at a rapid rate (200–300 mL/hr) to reverse intravascular volume contraction and promote renal excretion of calcium. Bedside vigilance to prevent fluid overload is essential. Loop diuretics are added to the regimen to reduce the risk of volume overload and inhibit calcium resorption in the loop of Henle. Patients with renal failure often cannot tolerate this large volume resuscitation; instead, they should be dialyzed with low-calcium dialysate (79).

Steroids lower calcium by inhibiting the effects of vitamin D (80). They also have been shown to decrease intestinal absorption of calcium, increase renal calcium excretion (81), and inhibit osteoclast-activating factor (82). Steroids are particularly effective in the setting of hypercalcemia secondary to granulomatous diseases, where hypercalcemia stems from vitamin D toxicity. The initial dose of hydrocortisone is 200–400 mg intravenously per day for 3–5 days (83). Steroids are ineffective in most cases of hypercalcemia associated with malignancy.

For the treatment of hypercalcemia of malignancy, efforts should include surgery, chemotherapy, and/or radiation therapy for the underlying cancer. Gallium nitrate, a compound that inhibits osteoclast resorption and lowers calcium, can be used at 200 mg/m² intravenously daily for 5 days. In this setting, gallium nitrate and pamidronate, a bisphosphonate, are equivalent in controlling hypercalcemia in small studies (84).

Calcitonin acts quickly (within 24–48 hrs) to lower serum calcium concentrations (85) and is more effective when used in combination with steroids (86). In a small, double-blind randomized trial of 50 cancer patients, however, calcitonin (8 IU subcutaneously daily for 5 days) was less effective than gallium nitrate (87). Preparations of calcitonin are manufactured from salmon. Patients with preformed antibodies to salmon, or who have had previous exposure to calcitonin, can demonstrate an allergic reaction that includes respiratory distress, flushing, nausea, vomiting, and tingling in the extremities (88).

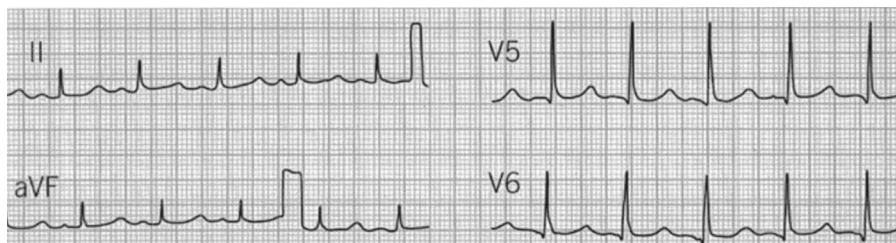


Figure 3. Electrocardiogram (EKG) consistent with hypocalcemia. This EKG demonstrates the prolonged QTc interval seen in hypocalcemia. Adapted with permission from Crawford M and DiMarco J. *Cardiology* 2001; 8(4.8), New York, Mosby.

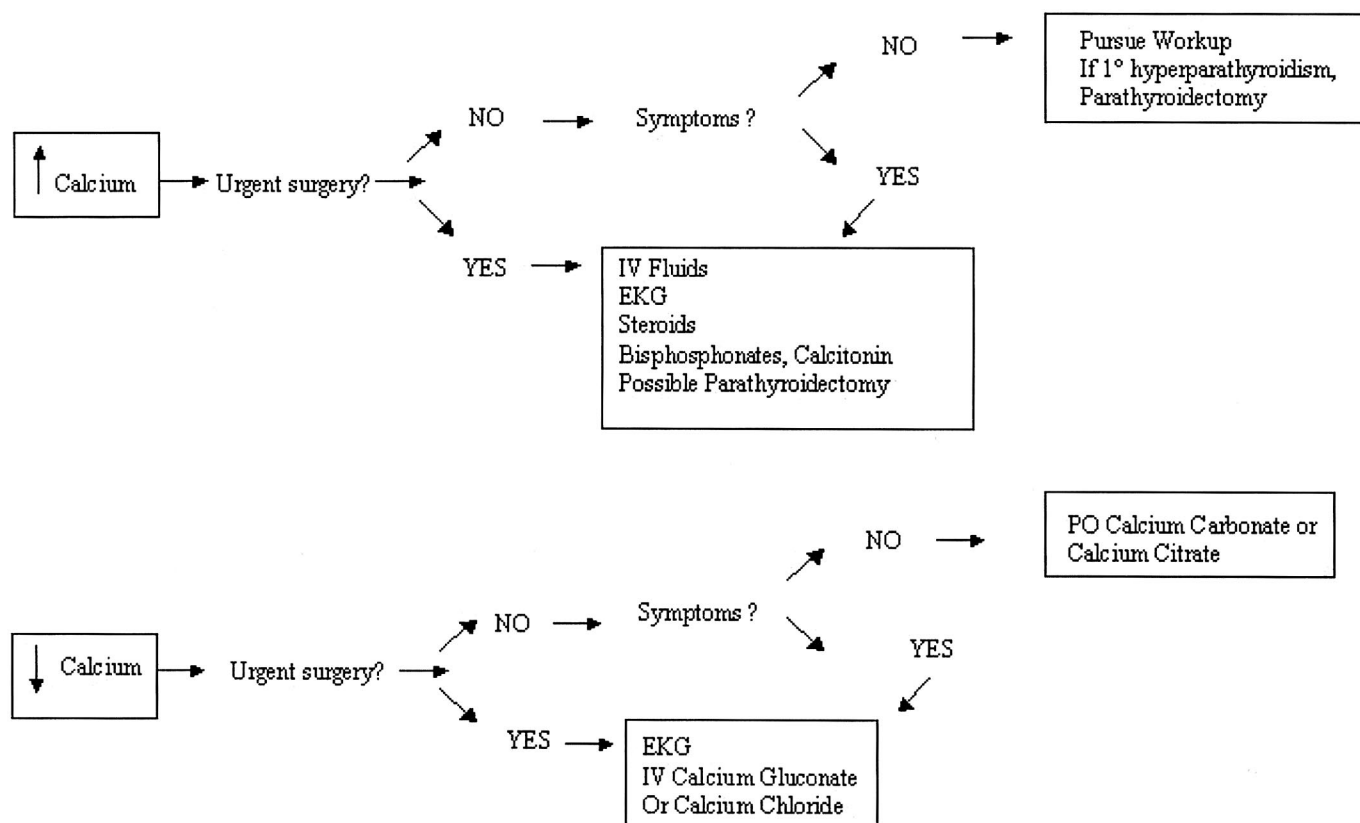


Figure 4. Management of calcium abnormalities. IV, intravenous; EKG, electrocardiogram; PO, oral.

Bisphosphonates are pyrophosphate analogs that have a high affinity for hydroxyapatite in bone. They potently inhibit osteoclast activity for up to a month. In the hypercalcemia of malignancy, pamidronate (90 mg intravenously) or zoledronic acid (4 mg intravenous initial treatment, 8 mg on retreatment) normalizes calcium concentrations in most patients (89). A single dose of a bisphosphonate lowers calcium concentrations, although recent evidence suggests that zoledronic acid might become the bisphosphonate of choice because of its rapid onset of action and its ability to lengthen the time to relapse two-fold; however, there also has been an association between zoledronic acid and compromised renal function (90).

If a patient is diagnosed with primary hyperparathyroidism, parathyroidectomy can achieve cure. Preoperative imaging studies localize the culprit glands, allowing surgeons to perform minimally invasive parathyroidectomy, that is, parathyroidectomy with a small incision (1–4 cm), local anesthesia, with unilateral neck exploration in an ambulatory setting. Sestamibi scan uses technetium-99m (^{99m}Tc), which diffuses into cells and

concentrates in the mitochondria. Cells with a high mitochondrial count will concentrate ^{99m}Tc and intensify on sestamibi scan (91). Parathyroid adenomas have a generous blood supply, a high metabolic rate, and an absence of p-glycoprotein on the cell surface, which allows for a rich uptake of ^{99m}Tc (92). When combined with single photon emission computed tomography, sestamibi is an especially powerful tool because it allows for three-dimensional localization. Ultrasound of the neck is often combined with sestamibi to exclude underlying thyroid abnormalities, which can distort sestamibi findings. The combined specificity of the two studies is >90%.

Parathyroidectomy is curative and safe in the hands of experienced surgeons. The rate of complications is as low as 1.2%, and cure rates are as high as 98% (93). Parathyroidectomy also can safely be done in patients >80 yrs of age (94). A National Institutes of Health consensus panel in 2002 specified the indications for surgery in primary hyperparathyroidism (Table 1).

Case Study. An extreme example of hypercalcemia associated with necrotizing pancreatitis that necessitated urgent

parathyroidectomy is described. Recently at our institution, a 51-yr-old man presented with severe abdominal pain and an abdominal computed tomography scan demonstrated necrotizing pancreatitis (Fig. 5, *top*). The patient was found to be hypercalcemic, with a total serum calcium concentration of 14.5 mg/dL, which was believed to be the cause of his pancreatitis. The patient was volume-resuscitated in the intensive care unit, and lasix, pamidronate, and calcitonin were administered. These measures transiently reduced the calcium concentration to 11 mg/dL. Workup for primary hyperparathyroidism revealed an intact PTH concentration of 887 pg/mL, and a neck ultrasound (Fig. 5, *bottom*) demonstrated a solitary parathyroid adenoma in the left inferior neck. A sestamibi scan confirmed localization. After hemodynamic stability was achieved, urgent parathyroidectomy was performed. The intraoperative PTH concentration decreased from 887 pg/mL to 130 pg/mL 15 mins after removal of the gland. On postoperative day 1, the PTH concentration was 37 pg/mL, demonstrating cure.

Hypocalcemia. Patients with hypocalcemia who are clinically stable can re-

Table 1. National Institutes of Health consensus panel recommendations for surgical intervention for primary hyperparathyroidism

Measurement	Threshold for Surgical Intervention
Serum calcium	1.0 mg/dL above the accepted normal range
24-hr urinary calcium	>400 mg
Creatinine clearance	Reduction of >30% compared with age-matched controls
Bone density	Reduced <2.5 standard deviations below the <i>t</i> score
Age	<50 yrs of age with primary hyperparathyroidism
Physical examination	Presence of symptoms (e.g., nephrolithiasis, pathologic fractures, pancreatitis)

Adapted from Belezikian J et al: Summary statement from a workshop on asymptomatic primary hyperparathyroidism: A perspective for the 21st century. *J Clin Endocrinol* 2002;87:5353–5361

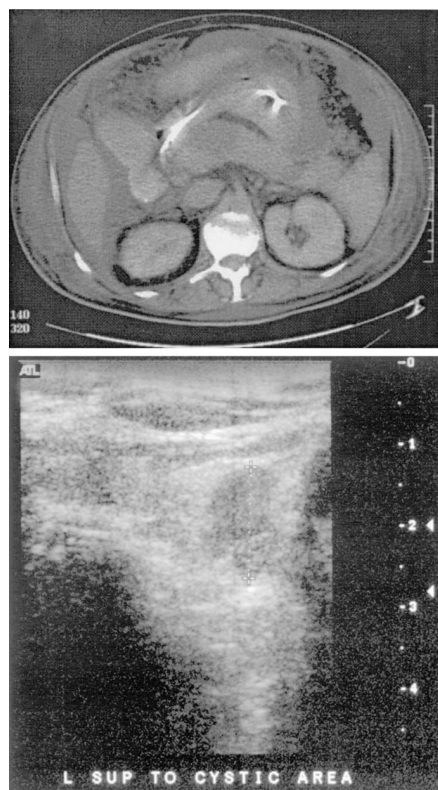


Figure 5. Top, computed tomography scan showing necrotizing pancreatitis. Bottom, ultrasound demonstrating left inferior parathyroid adenoma (see measure area).

ceive oral calcium. There has been debate about whether calcium carbonate or calcium citrate provides better calcium concentrations. Some studies have suggested that calcium citrate has better bioavailability (95). However, a recent randomized trial found no statistical difference. Calcium carbonate is less expensive (96). In addition, in uremic patients it is best to use calcium carbonate (97, 98). Calcium citrate should be administered to patients with achlorhydria who do not efficiently absorb calcium carbonate (99).

In emergent situations, 100–200 mg of calcium can be given intravenously as

a bolus, and a central vein should be used whenever possible. One milliliter of calcium chloride provides 27 mg of elemental calcium, and 1 mL of calcium gluconate gives 9 mg (100). Calcium chloride elevates the calcium concentration after plasmapheresis for longer periods (101) and is the historically favored calcium replacement because there is a higher dose of elemental calcium in 1 mL. In liver transplantation, calcium chloride or calcium gluconate can elevate calcium concentrations and even in surgery when the liver is *ex vivo* (102). *In vitro* and animal studies have not shown a difference in calcium ionization between the two intravenous preparations (103). In addition, there have not been data to support a difference during cardiac arrest (104). Either preparation can be administered, with knowledge that different amounts of calcium are present in the same volume.

Anesthetic Considerations. In patients with potentially unstable calcium concentrations, intraoperative measurements should be obtained as deemed indicated. In addition to its effects on major organ systems, hypercalcemia may increase the amount of anesthesia required for neuromuscular blockade with vecuronium (105).

Propofol lowers ionized calcium concentrations. This has not been shown to have clinically significant adverse effects, but high-risk patients with cardiac or endocrine problems have not been studied in detail (106). Propofol prevents intracellular calcium flux, resulting in increased time for platelet aggregation *in vitro*. The clinical relevance of this finding is unclear, since bleeding time is stable (107). In addition, propofol has been shown to elevate serum PTH concentrations by as much as 40% at high doses (200 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) in normal volunteers (108). The effect on patients with endocrinopathies is unknown.

Calcium is essential to homeostasis and the function of multiple organ systems, so it is prudent to monitor calcium concentrations before, during, and after surgery.

CONCLUSIONS

Calcium is essential to homeostasis and the function of multiple organ systems, so it is prudent to monitor calcium concentrations before, during, and after surgery. Abnormalities in calcium metabolism may be secondary to parathyroid pathology or might be a harbinger of other underlying conditions, such as neoplasia or granulomatous diseases. Diagnostic evaluation should ensue. Management strategies depend on the severity of clinical symptoms and the urgency of the underlying medical conditions. Patients who require urgent surgery can be taken to the operating room with careful intraoperative and postoperative monitoring, and calcium concentrations can be maintained with medical management. Elective surgery can be deferred until workup of the calcium derangement is complete. If there is a severe calcium derangement, patients should be resuscitated in a monitored setting, and in the case of hypercalcemic crisis, urgent parathyroidectomy might be required.

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