

Evaluation and management of hypercalcemia

Your patient has hypertension, osteoporosis, and fatigue. Physical findings are normal and age-appropriate, but the lab results show a moderately elevated serum calcium level. Will you ignore it, watch it, or investigate further?

Erin Hutton, PA-C, MPAS

Patients with hypercalcemia—elevated serum calcium levels—used to present symptomatically, when they developed nephrolithiasis, nephrocalcinosis, osteopenia, or osteofibrosa cystica. Today, however, routine laboratory work reveals the condition in patients who are otherwise asymptomatic.¹ The total calcium level normally ranges from 8 to 10 mg/dL. Mild hypercalcemia exists when total serum calcium is 10.5 to 12 mg/dL; when levels are higher than 14 mg/dL, hypercalcemia is considered severe.² This condition affects women more often than men. It occurs in the general population in 1 of every 600 to 1,000 people, but it manifests in 1 of 200 hospital patients.³

Etiology

Primary hyperparathyroidism; malignancy; medications such as thiazide diuretics, antacids, and lithium; and vita-

mins A and D can all cause hypercalcemia. Other causes include familial hypocalciuric hypercalcemia (FHH), immobilization, renal insufficiency, and endocrine abnormalities such as hyperthyroidism, pheochromocytoma, and adrenal insufficiency. It is important to search for the primary etiology instead of treating individual symptoms. Familiarity with the broad differential diagnosis allows PAs to look first for easily correctable causes, such as a medication regimen that requires adjustment. If the imbalance persists, the PA must evaluate appropriate organ systems to determine the source and refer the patient to the appropriate specialist. Failure to recognize hypercalcemia's significance delays treatment and has deleterious effects on the body. In patients with malignancy, treatment delays can be life threatening.²

Overactive parathyroid glands Overactive parathyroid glands are the most common cause of hypercalcemia. These glands are located outside the thyroid capsule on the posterior surface of the four thyroid wings.⁴ Other ectopic parathyroid glands occasionally lie within the thyroid tissue or around the mediastinum.³ When serum calcium levels are low, these glands produce parathyroid hormone (PTH). PTH increases bone resorption and causes the renal tubules to reabsorb calcium and excrete phosphorus. It also indirectly raises serum calcium by stimulating the enzyme 1 α -hydroxylase, which increases vitamin D synthesis and calcium absorption from the GI tract.²

Malignancy The second most common cause of hypercalcemia is malignancy. Hematologic malignancies, squamous cell cancers, and adenocarcinomas pro-

The author works in the internal medicine/endocrinology division of Jefferson City Medical Group, Jefferson City, Mo. She has indicated no relationships to disclose relating to the content of this article.

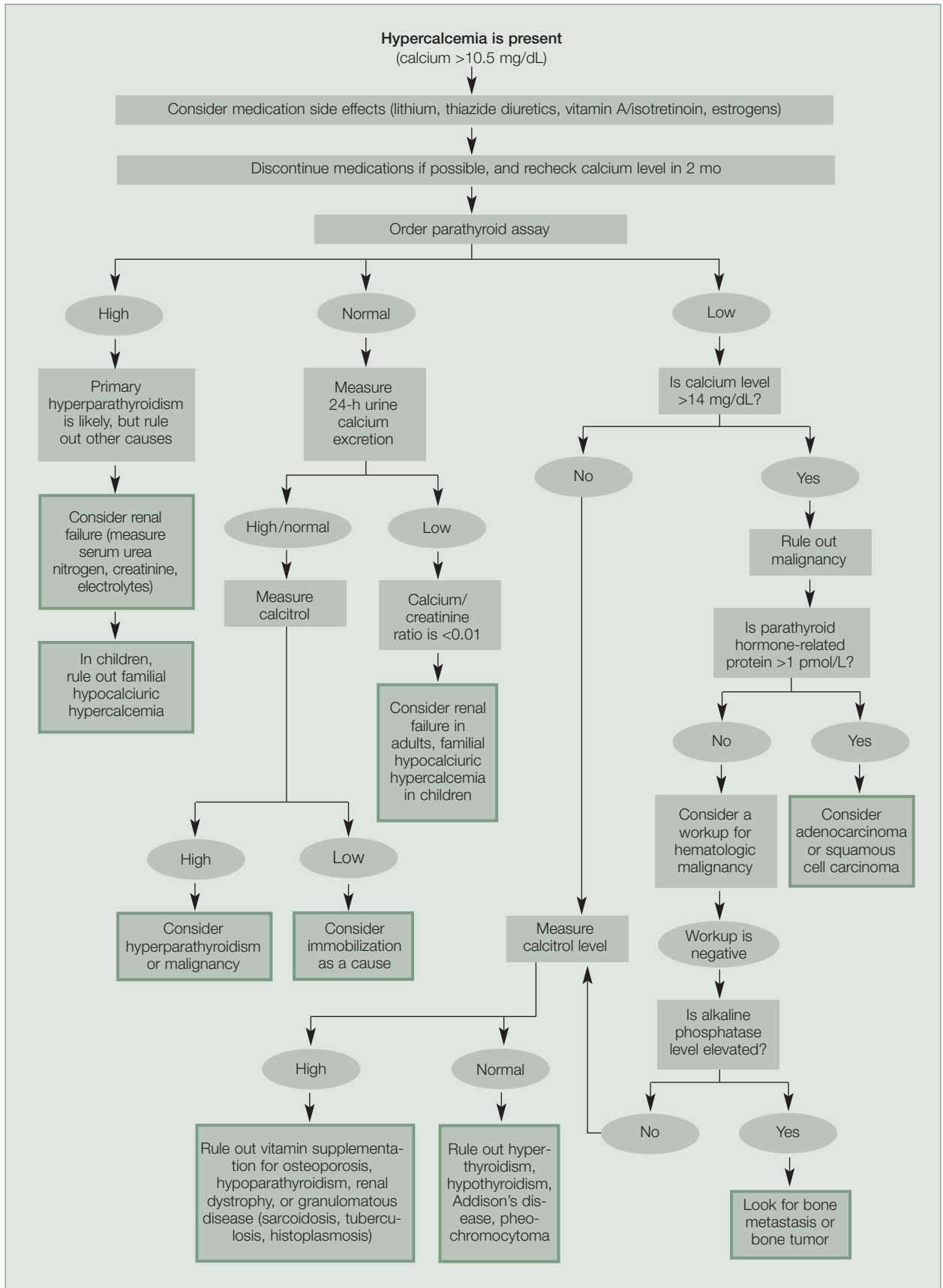
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Learning objectives

- Review the pathophysiology and symptoms of hypercalcemia
- Summarize the laboratory data needed to identify the cause
- Discuss therapeutic options for acute and chronic hypercalcemic states



duce parathyroid hormone-related protein (PTHrP), which has a terminal amino acid sequence similar to that of PTH.^{2,5} As a result, the protein can bind to PTH receptors and, again, renal tubules reabsorb calcium and excrete phosphorus, bone resorption increases, and vitamin D synthesis is initiated.^{2,3} Solimando reports that this humoral hypercalcemia of malignancy causes 80% of the hypercalcemia in patients with cancer.⁶

Vitamin D Toxicity from this vitamin is a less common cause of hypercalcemia. Physiologically, vitamin D increases the absorption of calcium and phosphorus in the GI tract and induces osteoclastic bone resorption, thereby causing a net increase in serum calcium.^{3,7}

History and physical examination

Since many causes of hypercalcemia produce similar symptoms without specific physical findings to differentiate them, a complete history and consideration of the patient's risk factors for each disease are essential. Information about first-degree relatives with hyperparathyroidism, endocrine disorders, or malignancies is especially relevant. Assess the risk of vitamin D toxicity by asking if the patient takes vitamin D supplements. In addition, because granulomatous disease can produce surplus vitamin D, it is helpful to know whether the patient has a history of sarcoidosis, tuberculosis, histoplasmosis, or silicone-induced granulomas.³

Patients with primary hyperparathyroidism and hypercalcemia of malignancy can be asymptomatic in mild disease. Both conditions disrupt calcium homeostasis and can produce similar symptoms, sometimes described as "bones, stones, abdominal groans, psychic moans, with fatigue overtones."^{6,8} However, red flags such as weight loss, anorexia, fever, and lethargy are highly suggestive of malignancy⁹ (see Table 1).

Bones Consider hypercalcemia when patients present with bone pain, gout, pseudogout, or pathologic fractures.^{2,8} The tissue composition of each bone determines how prone it is to fractures. The distal radius is comprised of cortical bone that is highly susceptible to resorption, while the vertebral spine is made of cancellous bone where PTH does not decrease bone density.^{1,3}

Kidneys Patients may present with nephrolithiasis, nephrocalcinosis, or hypercalciuria, which can compromise renal function and result in high serum creatinine.^{1,8} Patients occasionally develop nephrogenic diabetes insipidus, which is characterized by extreme thirst and urinary frequency. The body excretes excess calcium in the urine in order to maintain serum homeostasis, losing a large amount of water and becoming dehydrated in the process.^{2,8}

GI tract Common GI symptoms are abdominal pain, constipation, anorexia, nausea, or vomiting.^{8,10} Hyperparathyroidism can also cause acute pancreatitis.¹¹

KEY POINTS in this article

- ▶ Hypercalcemia is often found during routine laboratory work ordered on chronically ill patients who are still asymptomatic.
- ▶ Familiarity with the causes of hypercalcemia is essential, because certain types can be easily treated.
- ▶ If left untreated, hypercalcemia can adversely affect multiple organ systems, including the bones and kidneys.

Muscles and nerves Muscles may be weak, fatigued, or atrophied, and patients may report extremity paresthesias. In severe cases, they may be disoriented or comatose.^{2,8,11} The manifestations of psychic groans are decreased concentration, depression, and psychosis.⁸

Cardiovascular system Hypercalcemia can also cause hypertension, calcification of vasculature, arrhythmias, and short QT intervals.^{2,10}

Differential diagnosis The differential diagnosis of hypercalcemia is quite extensive (see Table 2, page 34, and the algorithm, page 31). Primary hyperparathyroidism and malignancy cause 85% to 90% of cases, so these conditions should be ruled out first.¹⁰

Laboratory testing

Laboratory findings are extremely useful in identifying the etiology of hypercalcemia. Total serum calcium levels higher than 12 mg/dL warrant further investigation; very high levels are suspicious for carcinoma.³ Phosphorus is low in primary hyperparathyroidism because it is excreted in the urine as calcium is reabsorbed in the renal tubules.¹² By contrast, phosphorus is not excreted in renal failure, so levels are high.⁹

Note that when serum albumin or pH is altered, total calcium may be an inaccurate reflection of physiologically active calcium. When calcium is bound to albumin, it is not physiologically active; thus, increased albumin results in less ionized physiologically active calcium. While measuring ionized calcium is most accurate, it is not a convenient procedure. The following equation can be used to correct the total calcium value so it accurately reflects physiologically active calcium: corrected calcium = [4.0 g/dL - (plasma albumin)] x 0.8 + (serum calcium).²

Hyperparathyroidism versus malignancy

The best way to distinguish between primary hyperparathyroidism and occult malignancy is to order a PTH level measured with an immunoradiometric or immunochemiluminometric assay. The PTH value is elevated in primary hyperparathyroidism but is usually low in malignancy.³

A PTHrP value that is greater than 1 pmol/L is a specific indicator for malignancy because it is not found in healthy people. Truong and colleagues investigated the use of PTHrP as a marker of malignancy and contend that it is of greatest value as a prognostic indicator in patients who have hypercalcemic malignancy and who are aged 65 years or younger. When these patients have an elevated PTHrP level, they have an approximately four-fold increase in mortality from malignancy over those younger than 65 without elevated PTHrP values.¹³

Other causes of elevated PTH levels

Lithium, thiazide diuretics, and certain medications used for renal failure can also cause elevated PTH levels.^{3,14} Malignancy in the lungs, ovaries, or thymus rarely does. The PTH level is low in almost all other cases of hypercalcemia.³

Vitamin D toxicity is distinguished from primary hyperparathyroidism by low serum PTH levels. In vitamin D toxicity, high serum calcium provides negative feedback on PTH production.²

FHH is most often seen in children, and PTH levels are usually normal. Measurement of 24-hour urinary calcium excretion and a ratio of calcium to creatinine of less than 0.01 can also distinguish FHH from primary hyperparathyroidism. While calcium excretion is high in primary hyperparathyroidism and immobilization, it is low in FHH.³

Hypercalcemia due to immobilization can be distinguished from primary hyperparathyroidism and malignancy using alkaline phosphatase and vitamin D levels. High bone turnover elevates alkaline phosphatase in most conditions, but levels are normal in cases of immobilization. Vitamin D levels are low in immobilization, but they are elevated in primary hyperparathyroidism because PTH induces vitamin D production.²

Hypercalcemia due to vitamin A toxicity can be diagnosed by measuring the total vitamin A level and the amount in the retinyl ester form.³

Bone density tests should be ordered for patients with asymptomatic hypercalcemia to determine how much bone mass has been lost and where.¹¹ A more aggressive therapeutic approach is warranted when the disease severely affects the bone.³

Treatment and follow-up

Acute care The most severe cases of hypercalcemia are caused by malignancies that elevate serum calcium levels beyond the kidneys' excretory capacity. As the kidneys excrete excess calcium and reabsorb less water, the body dehydrates, causing the glomerular filtration rate to decrease further and the serum calcium level to rise.¹² The first step is to replenish body fluids with 2 to 4 L of IV normal saline per day, after which furosemide can be

used to diurese excess fluid and calcium. When using this regimen, the clinician must carefully monitor magnesium and potassium values and fluid volumes to avoid complications. Thiazides are never used for diuresis because they increase serum calcium levels.

Once the patient is stable, prescribe calcitonin or pamidronate to prevent future episodes of hypercalcemia.^{15,16} Calcitonin is only useful for a few days to weeks because it rapidly decreases calcium levels and then loses its effect.^{12,17} Inject 4 to 8 units per kg of calcitonin IM or SC twice a day.^{12,17} Pamidronate, a bisphosphonate, is longer acting but has a slower onset than does calcitonin. It also occasionally causes fever. It is best to give acetaminophen before beginning the 24-hour infusion of 90 mg of pamidronate. After calcium levels return to normal in 4 to 7 days, give 30- to 60-mg maintenance doses every 2 weeks.¹²

Surgery The only curative therapy for symptomatic primary hyperparathyroidism is surgery. Consider it if the serum calcium level is greater than 12 mg/dL, if more

TABLE 1
Symptoms of hypercalcemia

Bone	
Fractures	Pain
Cardiac	
Arrhythmias	Shortened QT interval
Hypertension	Vascular calcification
Constitutional—red flags for malignancy	
Fever	Weight loss
Lethargy	
Gastrointestinal	
Abdominal pain	Nausea
Anorexia	Vomiting
Constipation	
Neurologic	
Coma	Seizures
Hyporeflexia	Tremor
Renal	
Polyuria	Renal stones
Renal insufficiency	
Data from Carroll MF and Schade DS, ² Solimando DA, ⁶ Tierney LM Jr et al. ³	

than 400 mg of calcium is excreted in the urine over 24 hours, or if a patient has renal insufficiency with decreased creatinine clearance. Other candidates for surgery have complications such as kidney stones, neuromuscular disease, or cortical bone density greater than two standard deviations below normal. Patients with acute attacks of hyperparathyroidism and those younger than 50 years should also have surgery.

Patients should be educated about the risks of parathyroidectomies. The recurrent laryngeal nerve can be severed and result in vocal cord paralysis. Hypoparathyroidism can occur when too much tissue is removed. If calcium levels remain high in the postoperative period, a second surgery may be necessary to look for small or ectopic parathyroid glands.¹

Asymptomatic hyperparathyroidism Some physicians argue that the long-term consequences of leaving asymptomatic hypercalcemia untreated are unknown and that surgery is the only way to prevent complications. However, the most popular approach manages these patients conservatively with biannual visits to their clinician. Serum calcium is measured and the clinician screens for disease complications. In addition, patients are instructed to remain well hydrated and active and to moderate their calcium intake. Consuming too

much calcium increases the risk of kidney stones, but low dietary calcium causes the parathyroid gland to release more PTH and further elevate serum calcium levels. The provider should evaluate bone density annually and collect a 24-hour urine sample to measure excreted calcium.¹¹

“Watchful waiting” also has its risks. The biggest challenge is maintaining adequate follow-up over an extended period. When patients fail to keep appointments, the disease can progress unnoticed until complications such as fatigue, kidney stones, bone cysts, or fractures develop.¹ Although most experts recommend close follow-up for asymptomatic persons, surgery is a better option if a patient is noncompliant and unlikely to keep scheduled appointments.¹

Malignancy The goals are to treat the cancer to eliminate tumor factors that alter calcium metabolism and to restore homeostasis.⁵ Medication can be used to lower dangerously elevated serum calcium levels in cases where treatment or its effects are delayed.⁵ When therapy for the cancer is effective, serum calcium levels usually decline.^{5,16} Unfortunately, malignancies that cause hypercalcemia are often advanced and do not respond well to therapy.¹⁶

Vitamin D toxicity The first step is to ensure that the patient is well hydrated;⁷ then administer 100 mg of hydrocortisone daily.⁹ Glucocorticoids inhibit vitamin D synthesis in the kidneys, cause the liver to produce more biologically inactive vitamin D, inhibit osteoclasts, and decrease intestinal absorption of dietary calcium.³ Dietary calcium and vitamin D should also be restricted.^{7,10}

Granulomatous diseases such as sarcoidosis should be treated in order to eliminate ectopic sources of vitamin D and reduce hypercalcemia.^{7,10} Patients with sarcoidosis must eliminate calcium supplements, avoid a calcium-rich diet, and forego prolonged sun exposure.^{7,10}

Administration of 20 to 40 mg of prednisone daily is the preferred pharmaceutical treatment for sarcoidosis to decrease vitamin D production and restore vitamin D and calcium levels to normal levels within 3 to 5 days. Once homeostasis is established, initiate a 4- to 6-week period of tapering the dosage of the corticosteroid, and carefully monitor serum and urine calcium levels.⁷ If the disease fails to improve or the therapy has side effects, use alternative therapies such as chloroquine, hydroxychloroquine, or ketoconazole.⁷ These medications diminish vitamin D and calcium levels, although ketoconazole may be less efficacious than the others.⁷

Pharmacotherapy Several pharmaceutical approaches to hypercalcemia are possible, although none is ideal. Oral phosphate decreases absorption of dietary calcium, blocks renal synthesis of vitamin D, and inhibits bone resorption. However, it is only prescribed in cases that are refractory to other treatment because it

TABLE 2

Differential diagnosis of hypercalcemia

- Chronic renal failure
- Endocrine disorders (hyperthyroidism, pheochromocytoma, Addison’s disease)
- Familial hypocalciuric hypercalcemia
- Immobilization
- Laboratory artifact due to altered albumin concentration or serum pH
- Malignancy (hematologic malignancies [non-Hodgkin’s lymphoma, multiple myeloma, leukemia], squamous cell carcinomas [lung, esophagus, cervix, vulva, skin], adenocarcinomas [breast, kidneys, ovaries, bladder], parathyroid carcinoma)
- Medications (vitamin A toxicity [dietary fads, isotretinoin overdose, multivitamin overdose], estrogens, antiestrogens, thiazides, lithium)
- Milk-alkali syndrome
- Primary hyperparathyroidism
- Vitamin D toxicity (granulomatous disease [sarcoidosis, tuberculosis], vitamin D supplementation)

Data from Chan FK et al,³ Potts JT,¹⁰ Olgaard K,¹⁴ Sato Y et al,¹⁵ Ziegler R,²² Moe SM and Druke TB,²⁵ George S and Clark JD,²⁶ Tal A and Powers K,²⁷ Muldowney WP and Mazbar SA.²⁸

reacts chemically with excess calcium, thereby calcifying vessels and organs.^{3,18}

In the past, estrogen was used to treat symptoms in postmenopausal women. Estrogen improves bone density and decreases bone resorption but does not affect elevated PTH or phosphorus levels.³ The Women's Health Initiative analyzed the effect of estrogen and progestin on the risk of fracture and bone mineral density. The authors concluded that the "results imply that the benefit of fracture reduction does not outweigh the risks of cardiovascular disease and breast cancer, even in women at higher risk for fracture."¹⁹

The bisphosphonates pamidronate and etidronate are the most beneficial pharmaceutical agents for treating hypercalcemia. They bind to bone minerals and are consumed by osteoclasts, which undergo apoptosis as the bisphosphonates interfere with their intracellular communication.^{5,20} In addition, bisphosphonates have deleterious effects on bone metastases by causing tumor cell apoptosis and altering their ability to invade the extracellular matrix of bone.²⁰ They also improve quality of life by reducing pain and decreasing the number of metastatic fractures. Clinically, bisphosphonates inhibit bone resorption, which occurs in hyperparathyroidism and malignancy.²⁰

To reduce hypercalcemia, etidronate is administered once only because it causes osteomalacia with further administration. Pamidronate is widely used, reduces hypercalcemia within 4 days, and is given every 2 weeks thereafter to maintain normal calcium levels.¹⁶ A newer bisphosphonate, zoledronic acid, has a faster onset, longer duration with improved pain relief, and greater patient response than pamidronate.^{5,20} It is infused over 15 minutes compared to several hours for pamidronate and has similar side effects.^{5,18}

Researchers have investigated calcimimetic agents, such as cinacalcet HCl (Sensipar), with promising results. These drugs act at parathyroid gland receptors, decreasing their sensitivity to calcium so that the gland releases less PTH. They show potential for treating hypercalcemia, although further research is needed.²¹

Once the clinician identifies the cause of hypercalcemia and initiates treatment, further follow-up is essential. Most often, hypercalcemia resolves when the underlying condition is treated. In rare instances when serum calcium levels remain elevated, however, the clinician must consider secondary causes of hypercalcemia. A patient may have primary hyperparathyroidism as well as an occult malignancy, for example.²² Patients should be educated regarding the wide variation of hypercalcemic symptoms and be advised to watch for them.

Prevention and patient education

Obtaining a family history is the most effective way to screen for potential hypercalcemia because a history of

endocrine disorders can help identify patients who are genetically predisposed. Multiple endocrine neoplasias, MEN I and II, are disorders in which multiple tumors develop and secrete hormones excessively.^{23,24} MEN I, and to a lesser degree, MEN IIA, are most closely associated with hyperparathyroidism.^{23,24} In children with hypercalcemia, it is important to ask about FHH, another genetic disorder. Failing to elicit a family history of FHH can result in the child undergoing surgery that will not cure the hypercalcemia.^{3,23} It is also important to ask patients about malignancies in their families and identify subtypes, since squamous cell cancers and adenocarcinomas are closely associated with hypercalcemia.^{2,5} Finally, patients on vitamin D therapy should understand the risk of overconsumption and be closely monitored for signs of hypercalcemia and toxicity.⁷ □

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