providers to understand basic terminology used by the trans community, which varies regionally.

Psychological and medical care must be provided in an environment that avoids preconceptions, and proper environmental signage, terminology, and staff training is essential (see WPATH Standards of Care). Accurate collection of gender identity information is also important; many organizations use a "two-step" method to collect these data: (1) gender identity and (2) sex listed on the original birth certificate, thus avoiding invisibility of transgender status.

Prior to a physical examination, history taking is necessary to understand an individual's anatomic changes associated with gender-affirming hormone therapy (GAHT) and surgical intervention. Secondary sex characteristics present on a wide spectrum of development in transgender patients. Providers should offer appropriate health maintenance and cancer screening based on an individual's anatomy.

GAHT is the most common medical intervention sought by transgender people and does not require subspecialty care. Primary care providers, gynecologists, and endocrinologists may prescribe this therapy. Treatment includes medications for hirsutism (spironolactone), contraception (estradiol/progestin), abnormal uterine bleeding (estradiol/progestins), menopause (estradiol/progestin), testosterone deficiency (testosterone), and benign prostatic hyperplasia (5-α reductase inhibitors).

GAHT must be patient-centered and individualized to the patient's goals. A discussion of the risks/benefits associated with treatment and informed consent are essential before beginning treatment. Criteria to consider before initiating GAHT include persistent, well-documented gender dysphoria, capacity to make a fully informed decision, age of majority in a given country, and if present, control of significant medical or psychological conditions. GAHT limits fertility, thus reproductive options should be discussed with patients prior to initiation of GAHT. Endocrine Society Clinical Practice Guidelines for GAHT are available. With GAHT, most physical changes occur over the course of 2 years, but the exact timeline of change is highly variable.

Feminizing hormone therapy is typically estradiol in combination with an androgen blocker. Goals are breast development; fat redistribution; and reductions in muscle mass, body hair, erectile function, sperm count, and testicular size. Estrogen therapy increases risk of deep venous thrombosis (DVT) and, to a lesser extent based on cohort study results, ischemic stroke and myocardial infarction; contraindications to estrogen therapy include a history of DVT, estrogen-sensitive neoplasm, and end-stage liver disease. Tobacco cessation should be encouraged prior to initiation of estrogen therapy due to increased risk of DVT. Anti-androgen therapy, such as spironolactone, diminishes secondary male sex characteristics and minimizes the estrogen dose needed, thus reducing risks associated with high-dose exogenous estrogen therapy. Monitoring testosterone and estradiol levels for adequate response to therapy is necessary for the first year.

Masculinizing hormone therapy is achieved using topical or injected testosterone with a goal of cessation of menses, facial hair growth, voice deepening, fat redistribution, increased muscle mass and body hair, and clitoral growth. Contraindications to testosterone therapy include pregnancy, unstable coronary artery disease, and polycythemia. Monitoring testosterone and estradiol levels for adequate response to therapy should occur for the first year. Hemoglobin also should be monitored.

Gender confirmation surgery is often the last intervention in transgender persons. Many transgender persons do not pursue surgery, but it is essential for alleviation of gender dysphoria in others. For transgender women, surgical procedures may include augmentation mammoplasty, genital surgery (penectomy, orchiectomy, vaginoplasty, clitoroplasty, vulvoplasty), and non-genital, non-breast surgery (facial feminization, voice surgery, thyroid cartilage reduction). For transgender men, surgical procedures may include mastectomy, hysterectomy with oophorectomy, phalloplasty, vaginectomy, scrotoplasty, and implantation of penile and/or testicular prostheses.

Stringent criteria must be met prior to undergoing irreversible gender reassignment surgery.

KEY POINTS

- Gender-affirming hormone therapy is the most common medical intervention sought by transgender people and does not require subspecialty care; criteria for gender-affirming hormone therapy include persistent, well-documented gender dysphoria, capacity to make a fully informed decision, age of majority in a given country, and if present, control of significant medical or psychological conditions.
- Screening and preventive medicine in transgender patients should be based on the individual's anatomy.

Calcium and Bone Disorders

Calcium Homeostasis and Bone Physiology

Regulation of serum calcium level is complex and dependent on the actions of vitamin D and parathyroid hormone (PTH). The primary effect of vitamin D is to enhance the absorption of calcium within the intestinal tract, whereas the effects of PTH are primarily mediated through regulation of calcium retention and excretion in the kidney (**Figure 15**). Measured calcium levels depend on the amount bound to albumin, which can be affected by nutrition and acid-base status. Hypoalbuminemia of any cause, such as cirrhosis or

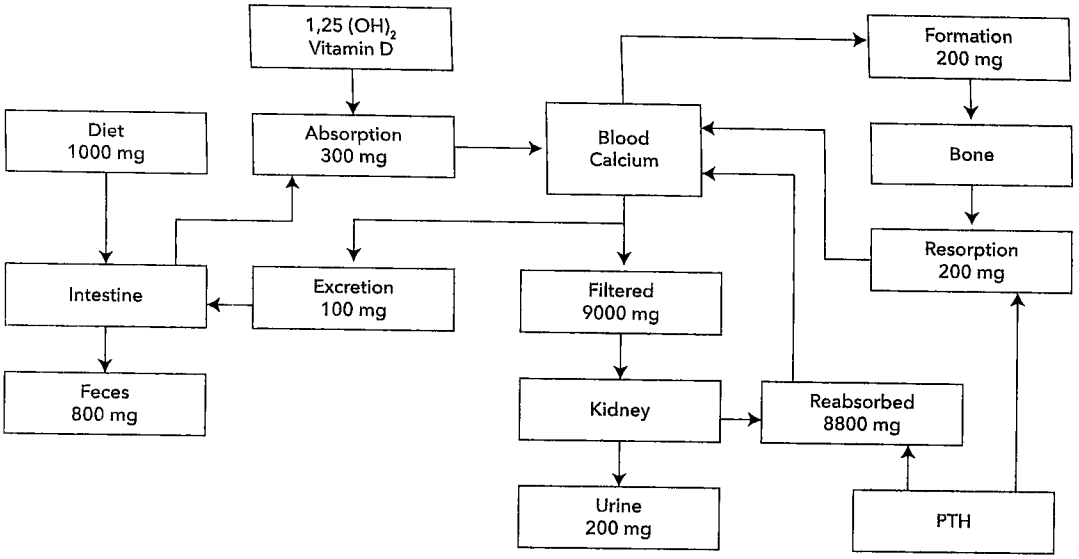

FIGURE 15. Neutral flux of calcium between bone and blood in adults is coordinated by parathyroid hormone (PTH). While most calcium filtered into urine is reabsorbed independent of PTH, PTH further increases retention of calcium from the urine. PTH indirectly augments calcium absorption in the gut by increasing production of 1,25 $(OH)_2$ vitamin D. Both effects of PTH are increasingly important at lower intakes of calcium and as blood levels of calcium decline. Amounts of calcium shown illustrate relative contribution of each organ to calcium homeostasis in a healthy adult.

malignancy-related cachexia, will cause low total calcium levels. When albumin concentration is low, measurement of ionized calcium or calculation of corrected total calcium is required to accurately assess calcium levels.

The level of vitamin D is determined by both production in the skin in response to sunlight and by ingestion, either from food or supplements. While vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol) are available as supplements, the latter may be more efficacious due to greater potency, longer half-life, and being identical to that formed from ultraviolet light exposure. Activation of vitamins D_2 and D_3 requires hydroxylation initially by the liver and subsequently by the kidney, resulting in the active form of vitamin D, 1,25-dihydroxyvitamin D, calcitriol. 25-Hydroxyvitamin D is the storage form of vitamin D in the body, and measurement of 25-hydroxyvitamin D is the most appropriate test for assessing vitamin stores.

The initial response to a decline in serum calcium is an increase in PTH secretion, which decreases renal calcium excretion and increases calcium resorption from the bones to raise the serum calcium level. PTH also induces increased renal conversion of 25-hydroxyvitamin D to the active metabolite 1,25-dihydroxyvitamin D, which improves the efficiency of intestinal calcium absorption. Continued PTH-mediated mobilization of calcium from bone over months to years in response to chronic negative calcium balance can lead to metabolic bone disease. In contrast, the skeleton, gut, and vitamin D metabolism do not significantly contribute to the correction of hypercalcemia. Instead, an increased filtered load and suppression of PTH secretion leads to robust excretion of calcium by the kidneys provided that effective circulating volume is adequate.

In addition to its role in mineral metabolism, the adult skeleton provides a reservoir of calcium, structural support for mobility, muscle attachment, and protection of vital organs. Bone remodeling allows for continuous skeletal adaptation and repair. Osteocytes coordinate bone remodeling, which is initiated by osteoclastic resorption then followed by much slower osteoblastic bone formation and mineralization of a collagen/protein matrix. The entire skeleton is remodeled approximately every 10 years.

KEY POINTS

- The primary effect of vitamin D is to enhance the absorption of calcium within the intestinal tract, whereas the effects of parathyroid hormone are primarily mediated through regulation of calcium retention and excretion in the kidney.
- Measurement of 25-hydroxyvitamin D is the most appropriate test for vitamin D deficiency.

Hypercalcemia

Clinical Features of Hypercalcemia

Hypercalcemia is diagnosed when the calcium level exceeds normal levels, typically 10.5 mg/dL (2.6 mmol/L). Incidental finding of asymptomatic hypercalcemia on routine or screening blood tests is common.

Classic symptoms of hypercalcemia include polyuria, polydipsia, and nocturia. Additional symptoms may include anorexia, nausea, abdominal pain, constipation, and mental status changes. At higher levels, patients may become obtunded. Symptoms do not correlate linearly with serum calcium or PTH levels.

Severe hypercalcemia and hypercalciuria can lead to volume depletion and acute kidney injury, nephrolithiasis, or nephrocalcinosis. Skeletal manifestations reflect the underlying cause of hypercalcemia. Primary hyperparathyroidism may present as osteoporosis with fragility fractures and low bone density. Severe hyperparathyroidism from parathyroid carcinoma or secondary hyperparathyroidism due to kidney disease may be associated with bone pain and osteitis fibrosa cystica (a radiographic diagnosis). Hypercalcemia associated with lytic bone lesions is often the result of multiple myeloma or breast cancer.

KEY POINT

- Symptoms of hypercalcemia are variable but may include polyuria, polydipsia, nocturia, anorexia, nausea, abdominal pain, constipation, and mental status changes, and they may be associated with acute kidney injury, nephrolithiasis, nephrocalcinosis, and skeletal changes.

Causes and Diagnosis of Hypercalcemia

Clues to the underlying cause of hypercalcemia include the severity, acuity of illness, and patient factors including concurrent illnesses. Hypercalcemia is categorized as mild (<12 mg/dL [3 mmol/L]), moderate (12-14 mg/dL [3-3.5 mmol/L]), or (severe >14 mg/dL [3.5 mmol/L]). When hypercalcemia is incidentally noted, repeat measurement is indicated. If hypercalcemia is confirmed, simultaneous measurement of serum calcium and PTH is a critical first step in diagnosing the cause and categorizing PTH-mediated and non-PTH-mediated hypercalcemia. Ionized calcium measurement is not helpful when the serum albumin level is normal or when there are no acute acid-base disorders. A thorough history and physical examination, as well as careful review of all medications including supplements, should be done in all patients with hypercalcemia.

KEY POINT

- Initial diagnostic testing for hypercalcemia requires simultaneous measurement of serum calcium and parathyroid hormone (PTH), which allows classification as PTH-related and non-PTH-related disease.

Medications Causing Hypercalcemia

Thiazide diuretics may cause mild hypercalcemia, especially in the setting of previously unrecognized, mild primary hyperparathyroidism. Hypercalcemia associated with lithium therapy is due to altered PTH secretion and may occur years after initiation of therapy. If possible, stopping the medication and rechecking calcium levels is a reasonable first step in management. If the calcium returns to normal, this suggests the medication was responsible.

Parathyroid Hormone–Mediated Hypercalcemia

PTH secretion decreases abruptly in response to a rise in serum calcium concentration. Therefore, an elevated or inappropriately normal (usually in the upper half of the reference range) PTH level in a patient with hypercalcemia is diagnostic of PTH-mediated hypercalcemia (**Figure 16**). Patients with an elevated PTH level but normal levels of calcium and vitamin D (normocalcemic primary hyperparathyroidism) may be managed similarly to those with asymptomatic primary hyperparathyroidism.

Primary Hyperparathyroidism

Primary hyperparathyroidism is typically caused by a solitary parathyroid adenoma. Women are more often affected than men, with a peak incidence in the seventh decade of life. Hypercalcemia is usually mild (within 1 mg/dL [0.25 mmol/L] of the upper limits of normal) and may be intermittently normal. Hypercalciuria is present in up to 30% of patients. Since

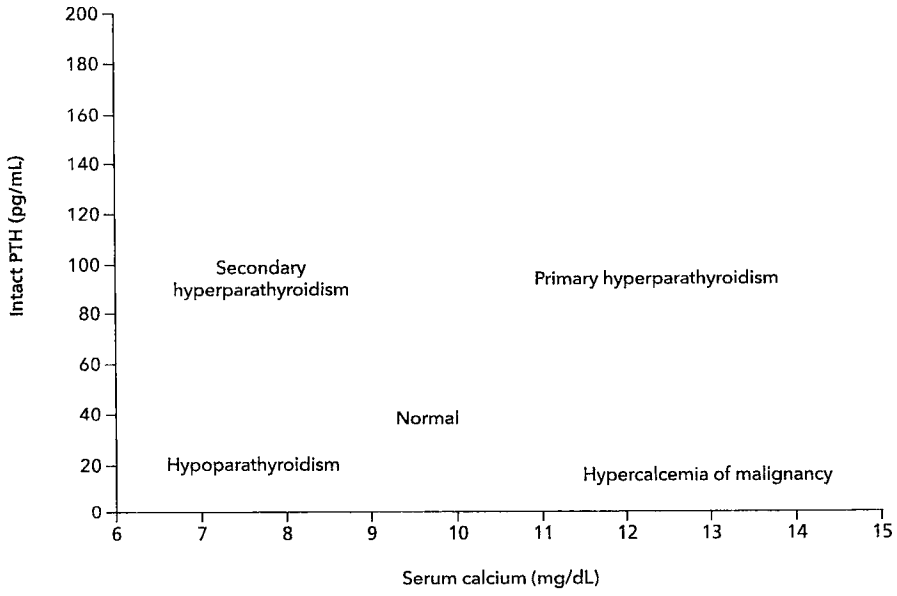

FIGURE 16. Relationship of calcium and parathyroid hormone (PTH) in normal conditions and in several diseases.

PTH enhances kidney phosphate excretion, low or low-normal serum phosphorus concentrations support the diagnosis. Assessment of bone mineral density (BMD) with dual-energy x-ray absorptiometry (DEXA) should include the nondominant forearm, which can be particularly affected in patients with hyperparathyroidism. Although parathyroid imaging with sestamibi or neck ultrasound may localize an adenoma, the presence of an adenoma does not influence the decision to proceed with surgery in the setting of primary hyperparathyroidism. Imaging may be beneficial to the surgeon for planning surgical intervention. In the absence of a history of calcium nephrolithiasis, kidney imaging may be indicated to exclude occult stones if this finding would change management.

Dietary calcium intake should be approximately 1000 mg/d to avoid further increases in urine calcium excretion and PTH secretion. Measurement of 25-hydroxyvitamin D and cautious correction of vitamin D deficiency is important. Repletion is recommended in patients whose levels are below 30 ng/dL (75 nmol/L) with careful attention to urine calcium excretion and serum calcium once vitamin D values are greater than 30 ng/dL (75 nmol/L).

Changes in specific endpoints during monitoring that lead to a recommendation for parathyroid surgery are outlined in **Table 43**. Surgery results in a 95% cure rate and less than 1% rate of complications with an experienced surgeon using minimally invasive techniques. Preoperative correction of vitamin D deficiency is important to avoid postoperative hypocalcemia, which is the result of relative hypoparathyroidism and reduced PTH-mediated production of 1,25-dihydroxyvitamin D culminating in a rapid flux of calcium into bone (hungry bone syndrome). Patients with mild primary hyperparathyroidism commonly require calcium supplementation for up to 1 week after parathyroidectomy until residual parathyroid tissue normalizes serum calcium concentrations. Reassessment of BMD 1 year after parathyroidectomy may show improvement in BMD, especially at the spine.

Approximately one in three patients with asymptomatic primary hyperparathyroidism who initially defer surgery will develop indications for surgery during 10 to 15 years of observation. In those not deemed eligible or who elect not to undergo surgery, evaluation should include annual measurement of serum calcium, creatinine, and glomerular filtration rate (GFR). If kidney stones are suspected, imaging and 24-hour urine collection for biochemical stone profile should be considered. BMD should be obtained every 2 years, and spine imaging should be considered if the patient has significant loss of height or back pain in the setting of a normal BMD.

KEY POINT

- Measurement of 25-hydroxyvitamin D and cautious correction of vitamin D deficiency is important in patients with primary hyperparathyroidism.

TABLE 43. Indications for Parathyroid Surgery During Monitoring

Assessment	Indication[a]
Serum calcium (>upper limit of normal)	>1 mg/dL (>0.25 mmol/L)
Skeletal	T-score <−2.5 at lumbar spine, total hip, femoral neck, or distal 1/3 radius; or a significant reduction in BMD[a]
	Vertebral fracture by x-ray, CT, MRI, or VFA
Renal	CrCl <60 mL/min
	Clinical development of a kidney stone or by imaging (x-ray, ultrasound, or CT)

CrCl = creatinine clearance; MRI = magnetic resonance imaging; VFA = vertebral fracture assessment.

[a]A significant change is defined by a reduction that is greater than the least significant change as defined by the International Society for Clinical Densitometry.

From Bilezikian JP, Brandi ML, Eastell R, Silverberg SJ, Udelsman R, Marcocci C, et al. Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism: Summary Statement from the Fourth International Workshop. J Clin Endocrinol Metab. 2014;99:3561-9. [PMID: 25162665]

Parathyroid Carcinoma

Parathyroid carcinoma is very rare, but may present with symptoms of severe hypercalcemia, with serum levels greater than 14 mg/dL (3.5 mmol/L) and markedly high PTH concentrations. Imaging is not useful and fine-needle aspiration is not recommended due to concerns of tumor seeding. The primary treatment is surgical resection. Unfortunately, 50% of patients may have residual or recurrent disease. Severe hypercalcemia in parathyroid carcinoma that is not amenable to surgery can be treated chronically with cinacalcet. Medical management options are limited, and patients are most likely to die from complications of hypercalcemia.

Tertiary Hyperparathyroidism

In patients with end-stage kidney disease, multigland hyperplasia results from chronic stimulus of PTH (a sequela of long-standing secondary hyperparathyroidism) due to poorly controlled hypocalcemia and hyperphosphatemia. In some cases of secondary hyperparathyroidism, the serum calcium can normalize if the hyperplasia and associated PTH secretion is robust. Chronic stimulation of the parathyroid glands can lead to autonomous production of PTH by all four glands, resulting in hypercalcemia. Tertiary hyperparathyroidism is most commonly recognized after kidney transplantation. Although historically treated with subtotal multigland parathyroidectomy, the hypercalcemia can be resolved in most patients by treatment with paricalcitol or cinacalcet.

Genetic Causes of Hypercalcemia

Familial Hypocalciuric Hypercalcemia

Familial hypocalciuric hypercalcemia (FHH) is an autosomal dominant condition and the most common type of familial hypercalcemia. Patients are asymptomatic. The parathyroid glands and kidney detect serum calcium concentrations

through the calcium-sensing receptor (CaSR). In FHH, inactivating mutation of the CaSR gene causes the parathyroid gland to perceive serum calcium concentrations as low, resulting in increased PTH secretion and a higher serum calcium level. Simultaneously, the mutated CaSR in the kidney increases kidney reabsorption of calcium, leading to paradoxical hypocalciuria in the setting of hypercalcemia.

Although these patients appear to have primary hyperparathyroidism, FHH is a benign condition that is not treated with parathyroidectomy. Hypercalcemia will not resolve with surgery. Patients do not have sequelae of hypercalcemia, such as stones or osteoporosis. Signs suggestive of FHH include: mild hypercalcemia since childhood; low 24-hour urine calcium excretion, especially if calcium-creatinine clearance ratio is below 0.01; and/or family history of parathyroidectomy without resolution of hypercalcemia. If clinically ambiguous, the diagnosis can be confirmed by CaSR genetic testing.

KEY POINT

- The distinction between primary hyperparathyroidism and familial hypocalciuric hypercalcemia can be made by a 24-hour urine collection for calcium and creatinine, which will establish the amount of kidney calcium excretion and will allow evaluation of the calcium-creatinine clearance ratio.

Multiple Endocrine Neoplasia Syndrome

Primary hyperparathyroidism in adolescents and young adults may be the first sign of multiple endocrine neoplasia syndrome (MEN). Primary hyperparathyroidism is associated with MEN1 and MEN2A syndromes. If the family history reveals primary hyperparathyroidism, pituitary tumor, Zollinger-Ellison syndrome, early death from pancreatic neoplasm, pheochromocytoma, or medullary thyroid cancer, MEN is more likely and screening should be considered. In contrast to sporadic primary hyperparathyroidism, MEN syndromes have recurrence of hyperparathyroidism due to ongoing hyperplasia in the remaining parathyroid tissue after parathyroidectomy. MEN1 is associated with mutation of the tumor suppressor *MEN1* gene, and MEN2A is associated with mutation of the *RET* gene. This is best managed in conjunction with or by an endocrinologist.

Non-Parathyroid Hormone-Mediated Hypercalcemia

The differential diagnosis of hypercalcemia with suppressed PTH is broad. In patients with severe hypercalcemia, the history, symptoms, and findings may suggest the underlying cause. Treatment should commence without delay while awaiting results of laboratory testing. In PTH-independent hypercalcemic states, hypercalciuria can be severe and may precede hypercalcemia. PTH is usually undetectable but may be very low (<20 pg/mL [20 ng/L]) if hypercalcemia is mild.

Malignancy-Associated Hypercalcemia

The most common cause of non-parathyroid hormone-mediated hypercalcemia is malignancy, and it is typically severe (>14 mg/dL [3.5 mmol/L]). It is often the result of tumor-produced PTH related protein (PTHrP) leading to extensive resorption of bone. Renal cell carcinoma, breast cancer, and squamous cell cancers are associated with PTHrP-related hypercalcemia. Rarely, locally mediated osteolysis from extensive skeletal metastases, typically in multiple myeloma and breast cancer, may cause efflux of calcium from bone resulting in significant hypercalcemia. For more information, see MKSAP 18 Hematology and Oncology.

Vitamin D–Dependent Hypercalcemia

Vitamin D–dependent hypercalcemia is associated with normal to elevated serum phosphorus levels because vitamin D enhances intestinal absorption of phosphorus and suppressed PTH secretion reduces kidney phosphorus excretion.

Unregulated conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D may occur in granulomatous tissue associated with fungal infection, tuberculosis, sarcoidosis, and lymphoma, leading to increased intestinal absorption of calcium. These conditions are associated with an inappropriately normal or frankly elevated 1,25-dihydroxyvitamin D level and suppressed PTH. Decreased serum and urine calcium after intake of calcium and vitamin D is restricted or a rapid decrease in calcium after glucocorticoid therapy (which inhibits the hydroxylation of 25-hydroxyvitamin D) is consistent with these disorders.

Vitamin D intoxication from chronic high-dose ingestion of vitamin D (typically >50,000 units daily in patients without malabsorptive conditions) and increased storage in fat causes protracted hypercalciuria, nephrolithiasis, impaired kidney function, and elevated 25-hydroxyvitamin D levels.

Other Causes

Ingestion of large amounts of calcium typically from antacid use (for example, calcium carbonate), especially with coexistent chronic kidney disease, causes milk-alkali syndrome.

Glucocorticoid and mineralocorticoid replacement and volume repletion resolve the mild hypercalcemia sometimes associated with Addisonian crisis.

Severe thyrotoxicosis occasionally causes hypercalcemia or hypercalciuria by increasing bone resorption.

Acute prolonged immobilization, as seen in spinal cord injuries, can cause large efflux of calcium from the skeleton through uncoupled bone remodeling with decreased osteoblastic activity despite increased osteoclastic activity. Patients with primary hyperparathyroidism or skeletal metastases are predisposed to hypercalcemia due to immobilization as are young patients where increased bone remodeling is normal.

Management of Hypercalcemia

Management is dependent on the severity of the hypercalcemia. If mild (<12 mg/dL [3 mmol/L]), treatment of the underlying disorder (for example, parathyroidectomy in primary hyperparathyroidism) is sufficient. Hospitalization

may be needed in patients with acute kidney injury, mental status changes, or calcium levels above 12 mg/dL (3 mmol/L). Initial treatment of severe hypercalcemia is aggressive hydration to replete volume loss and increase kidney excretion of calcium. Loop diuretics are not recommended unless kidney failure or heart failure is present, in which case volume expansion should precede the administration of loop diuretics to avoid hypotension and further kidney injury. For the acutely symptomatic patient, subcutaneous calcitonin can be used; however, the drug effect wanes after 48 hours. Long term management of hypercalcemia may require intravenous bisphosphonate therapy to prevent mobilization of calcium from the skeleton, but requires adequate kidney function. Glucocorticoids and restriction of calcium and vitamin D intake are uniquely beneficial in vitamin D dependent hypercalcemia. Hemodialysis is reserved for the treatment of severe hypercalcemia in oliguric patients.

KEY POINT

- Initial treatment of moderate to severe hypercalcemia is aggressive hydration to replete volume loss and increase kidney excretion of calcium; loop diuretics are not recommended unless kidney failure or heart failure is present, in which case volume expansion should precede the administration of loop diuretics to avoid hypotension and further kidney injury.

Hypocalcemia

Clinical Features of Hypocalcemia

Signs and symptoms of hypocalcemia reflect its severity and acuity. Hypocalcemic disorders in outpatients are typically detected on screening blood tests and are mild, with serum calcium 7.5 to 8.9 mg/dL (1.9-2.2 mmol/L). It may also be detected during evaluation for low-intensity traumatic fractures or low bone mass. Most patients will be asymptomatic or report symptoms of intermittent paresthesia of the hands and feet or perioral numbness. Hypocalcemia due to chronic hypoparathyroidism can also be associated with cataract formation, basal ganglia calcification, papilledema, and dental enamel hypoplasia.

Patients with severe hypocalcemia may present with neuromuscular symptoms and signs. Carpopedal spasm with characteristic hand posture (flexion at metacarpophalangeal joints and extension at interphalangeal joints) may be spontaneous or triggered by transient distal limb ischemia during blood pressure assessment (Trousseau sign). Facial nerve hyperirritability and muscle spasm can be demonstrated by percussion of the facial nerve just anterior to the ear (Chvostek sign). Importantly, laryngospasm, seizure, myocardial dysfunction, and QT-interval prolongation leading to sudden cardiac death due to severe hypocalcemia (<7.5 mg/dL [1.9 mmol/L]) can occur without prodromal paresthesia or muscle cramping.

KEY POINT

- Laryngospasm, seizure, myocardial dysfunction, and QT-interval prolongation leading to sudden cardiac death due to severe hypocalcemia (<7.5 mg/dL [1.9 mmol/L]) can occur without prodromal paresthesia or muscle cramping.

Causes and Diagnosis of Hypocalcemia

Hypocalcemia should be confirmed with a second measurement, which requires assessment of and correction for serum albumin concentrations. Ionized calcium measurement is indicated in the setting of fluctuating acid/base status. Simultaneous measurement of serum calcium, phosphorus, creatinine, and PTH is the next step. PTH should be elevated in the setting of hypocalcemia (see Figure 16).

Hypoparathyroidism

Hypoparathyroidism is most commonly caused by inadvertent injury during anterior neck surgery (thyroidectomy, parathyroidectomy) or surgery to treat parathyroid gland hyperplasia, both of which present within a few hours of surgery. Depending on the extent of injury/resection, surgical hypoparathyroidism may last days to weeks. Permanent hypoparathyroidism may be partial or complete; the latter is associated with undetectable serum PTH levels and a higher prevalence of hyperphosphatemia.

Inappropriately normal PTH levels with concurrent hypocalcemia represents the former. Other causes of hypocalcemia due to insufficient PTH secretion include infiltrative disorders (hemochromatosis or Wilson disease), radiation, autoimmunity, and congenital disorders (such as 22q11.2 deletion syndrome). Chronic hypocalcemia with inappropriately normal PTH occurring within a family may represent an activating mutation of the *CaSR* gene. Hypomagnesemia, seen in the settings of malnutrition, alcoholism, and with use of loop diuretics and chronic proton pump inhibitor therapy, causes functional, reversible parathyroid hypofunction and must be excluded before a low or inappropriately normal PTH level is attributed to hypoparathyroidism. PTH resistance (pseudohypoparathyroidism) is a rare genetic cause of hypocalcemia.

KEY POINT

- Hypomagnesemia causes functional, reversible parathyroid hypofunction and must be excluded before a low or inappropriately normal parathyroid hormone level is attributed to hypoparathyroidism.

Other Causes of Hypocalcemia

Malnutrition and/or malabsorption of either or both vitamin D and calcium may be suspected based on clinical history (bariatric surgery, celiac disease) and confirmed by low serum 25-hydroxyvitamin D level or low 24-hour urine calcium excretion (a proxy indicator of calcium intake and absorption). The most common cause of acquired hypocalcemia is chronic

kidney failure due to impaired production of 1,25-dihydroxyvitamin D and hyperphosphatemia. Hypercalciuria is most often idiopathic, but can also be due to chronic loop diuretic use. Rhabdomyolysis and tumor lysis syndrome increase serum phosphorus and calcium phosphate binding in the vascular space, causing low ionized calcium.

Hungry bone syndrome (rapid flux of calcium into bone after parathyroidectomy for severe primary hyperparathyroidism) and widespread osteoblastic metastases (prostate cancer, breast cancer) can cause hypocalcemia, as can saponification of calcium (and magnesium) in necrotic fat in acute pancreatitis.

Potent antiresorptive drugs, such as intravenous bisphosphonates and denosumab, can cause severe and protracted hypocalcemia by impairing physiologic efflux of calcium from the skeleton in patients with vitamin D deficiency. Therefore, it is important to assess vitamin D levels and correct deficiency before beginning treatment with an antiresorptive drug.

Management of Hypocalcemia

Because severe neuromuscular complications of hypocalcemia can occur in the absence of prodromal muscle tetany, severe hypocalcemia (<7.5 mg/dL [1.9 mmol/L]) requires urgent treatment with intravenous calcium. Slow administration through central intravenous access with electrocardiographic monitoring is preferred. Alternatively, teriparatide 20 μg twice per day rapidly eliminates hypocalcemic symptoms in acute postsurgical hypoparathyroidism (off-label indication).

Vitamin D supplementation 1000 to 4000 IU/d and oral calcium carbonate or calcium citrate at doses of 1 to 3 g/d in divided doses may normalize or sufficiently treat mild or chronic hypocalcemia. Calcitriol is needed in the setting of hypoparathyroidism with undetectable PTH and kidney failure because 1,25-dihydroxyvitamin D activation requires both PTH and sufficient kidney function.

In chronic hypoparathyroidism, goals of therapy are to eliminate symptoms while avoiding complications of therapy. A reasonable goal for most patients is a serum calcium concentration at or just below the reference range without hypercalciuria. Monitoring of urine calcium excretion is mandatory because hypercalciuria often limits therapy. Correction of coexisting hypomagnesemia is also required. Thiazide diuretics are commonly used because they decrease urine calcium excretion.

Initial treatment of hyperphosphatemia is reduction of dietary phosphorus but occasionally requires the addition of oral phosphate binders if serum phosphorus exceeds the normal range. Recombinant human PTH is available for patients who do not meet treatment goals with calcium and calcitriol therapy alone.

KEY POINT

- A reasonable goal for most patients with hypoparathyroidism is a serum calcium concentration at or just below the reference range without hypercalciuria.

Metabolic Bone Disease

Low Bone Mass and Osteoporosis

Bone mass, mineral content, and macro- and microarchitecture determine bone strength. Bone mineral density (BMD) reflects bone mass and mineral content and, in older adults, predicts deterioration of microarchitecture. This relationship and epidemiologic data underpin the use of BMD determined by dual-energy x-ray absorptiometry (DEXA) to diagnose low bone mass and refine fracture risk assessment in older adults. Fragility fractures (those occurring with minimal trauma, equivalent or less than a fall from a standing height) after age 50 indicate low bone strength and define clinical osteoporosis regardless of BMD. Skull, feet, and hand fractures cannot, by definition, be fragility fractures.

Pathophysiology

Low bone mass in adults may represent poor bone formation, bone loss, or both. Factors that can affect peak bone mass formation include genetic conditions, lifestyle factors, and poor health, especially in the second decade of life. Net loss of bone mass can occur in adults when osteoclastic bone remodeling is faster than osteoblastic bone formation. The list of risk factors for low bone mass and osteoporosis is extensive and is included in **Table 44** and **Table 45**. Some patients, however, have osteoporosis caused by secondary causes. Testing for secondary causes is summarized in **Table 46**.

Screening for Osteoporosis

Current guidelines recommend screening average risk postmenopausal women beginning at age 65. Guidelines vary in their recommendations for routine screening for osteoporosis in men. The American College of Rheumatology recommends BMD testing within 6 months of starting long-term glucocorticoid therapy in adults 40 years of age and older and in adults under 40 years of age with risk factors for osteoporosis or a history of fragility fractures.

Patients with risk factors for low bone mass or osteoporosis, fragility fractures of the femur, vertebra (**Figure 17**), pelvis, humerus or radius, height loss of 4 cm (1.6 in) or more, or kyphosis, should have BMD testing earlier than standard screening recommendations. BMD may also be indicated if the risk of fractures is elevated based on the results of risk assessment tools such as the Simple Calculated Osteoporosis Risk Estimate (SCORE), Osteoporosis Self-Assessment Tool (OST), the Osteoporosis Risk Assessment Instrument (ORAI), and Fracture Risk Assessment Tool (FRAX). **Table 47** lists recommendations for BMD testing and vertebral imaging.

Screening of younger women may be indicated if one or more risk factors for osteoporosis are present. In premenopausal women without risk factors, assessment of BMD for fracture risk is not advised or validated. However, if testing is done in an otherwise healthy person, results that are below age- and gender-matched averages (Z-score <0) generally do not require further evaluation or serial monitoring.