CLINICAL PRACTICE

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Hypoparathyroidism

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

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A previously healthy 31-year-old woman began having progressive paresthesias and numbness of her hands, neck, face, and back, for which she was evaluated by her primary care physician and a neurologist, but no cause was identified. Her family history was notable for autoimmune thyroid disease in a parent and sibling and psoriasis in another sibling. Six months after the onset of symptoms, the patient had carpopedal spasms in her hands and feet during exercise, which rapidly progressed to difficulty breathing and full body tetany. On arrival at the emergency department, she was found to have hypocalcemia and hyperphosphatemia, with an undetectable parathyroid hormone level. How would you evaluate and treat this patient?

THE CLINICAL PROBLEM

An audio version of this article is available at NEJM.org

Hypoparathyroidism is a rare disorder of parathyroid hormone (PTH) deficiency, with an estimated prevalence of 23 to 37 cases per 100,000 person-years. It most commonly occurs as a complication of anterior neck surgery (in approximately 78% of cases) and is therefore seen more frequently in older adult women, who are more likely than others in the general population to undergo thyroid surgery.[1,2] However, there is an expanding list of genetic[3] and nonsurgical acquired causes, including autoimmune causes (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). PTH is critical for maintaining the level of circulating calcium within a narrow normal range through its actions on bone, kidney, and intestine. Its secretion is regulated primarily by the calcium-sensing receptor (CaSR) found on parathyroid chief cells; when ambient calcium levels are low, the CaSR is inactive and PTH synthesis and secretion are increased.[4] PTH then regulates calcium and phosphate levels by actions on the bone, kidney, and, indirectly, intestine (Fig. 1).

Most patients with hypoparathyroidism have neuromuscular signs and symptoms of hypocalcemia, ranging from mild paresthesias, muscle cramps, and prolongation of the corrected QT (QTc) interval to severe, life-threatening manifestations such as arrhythmias, laryngospasm, and seizures.[6] In some patients, particularly those with certain genetic forms of hypoparathyroidism, the hypocalcemia may be asymptomatic. Often a parent or older sibling is identified as having hypoparathyroidism after the diagnosis is made in a child.[7] Because there is a lack of PTH-mediated bone resorption, patients have low bone turnover, so over time, their bone mass increases.[8] However, the data on fracture risk among patients with this disorder vary. In some postsurgical hypoparathyroid cohorts, patients may have a decreased risk of fracture in the upper extremities,[9,10] whereas others have had an increased risk of vertebral fractures despite having normal or increased

KEY CLINICAL POINTS

HYPOPARATHYROIDISM

- Hypoparathyroidism is a rare disease that results in hypocalcemia. Symptoms, when present, range from paresthesias and muscle cramps to seizures and laryngospasm.
- The most common cause is injury to or removal of the parathyroid gland during anterior neck surgery. Other genetic or autoimmune causes may be isolated or part of a larger syndrome.
- Hypoparathyroidism is often associated with basal ganglia calcification, cataracts, and neuropsychiatric symptoms.
- The goal of treatment is to maintain the blood calcium level near the low end of the normal range while preventing symptoms of hypocalcemia; this is usually achieved with oral calcium and active vitamin D (calcitriol or alfacalcidol) supplementation but may involve treatment with subcutaneous parathyroid hormone therapy.
- Treatment is commonly associated with hypercalciuria, nephrocalcinosis, nephrolithiasis, and renal insufficiency, thus emphasizing the need for careful monitoring and improved therapies.

bone mineral density.[11] In patients with hypoparathyroidism with a nonsurgical cause, who often have other risk factors for fracture such as use of glucocorticoids and anticonvulsant agents, the fracture risk may be increased.[12,13]

Patients with hypoparathyroidism may have increased risks of infection and cardiovascular disease.[9,14] Basal ganglia calcification, although of uncertain clinical significance, has been reported in more than 50% of patients with hypoparathyroidism of varying causes and is thought to be mediated, in part, by chronic hyperphosphatemia.[15,16] Cataracts are also a feature of long-standing nonsurgical hypoparathyroidism.[9,17] Patients with nonsurgical hypoparathyroidism may have dental abnormalities, including enamel hypoplasia and hypodontia.[18] Many patients have a reduced quality of life, with nonspecific symptoms that can include general fatigue, a lack of focus (often referred to as "brain fog"), depression, and other neuropsychiatric issues.[9,19] Renal complications frequently develop and appear to be related to therapy.

STRATEGIES AND EVIDENCE

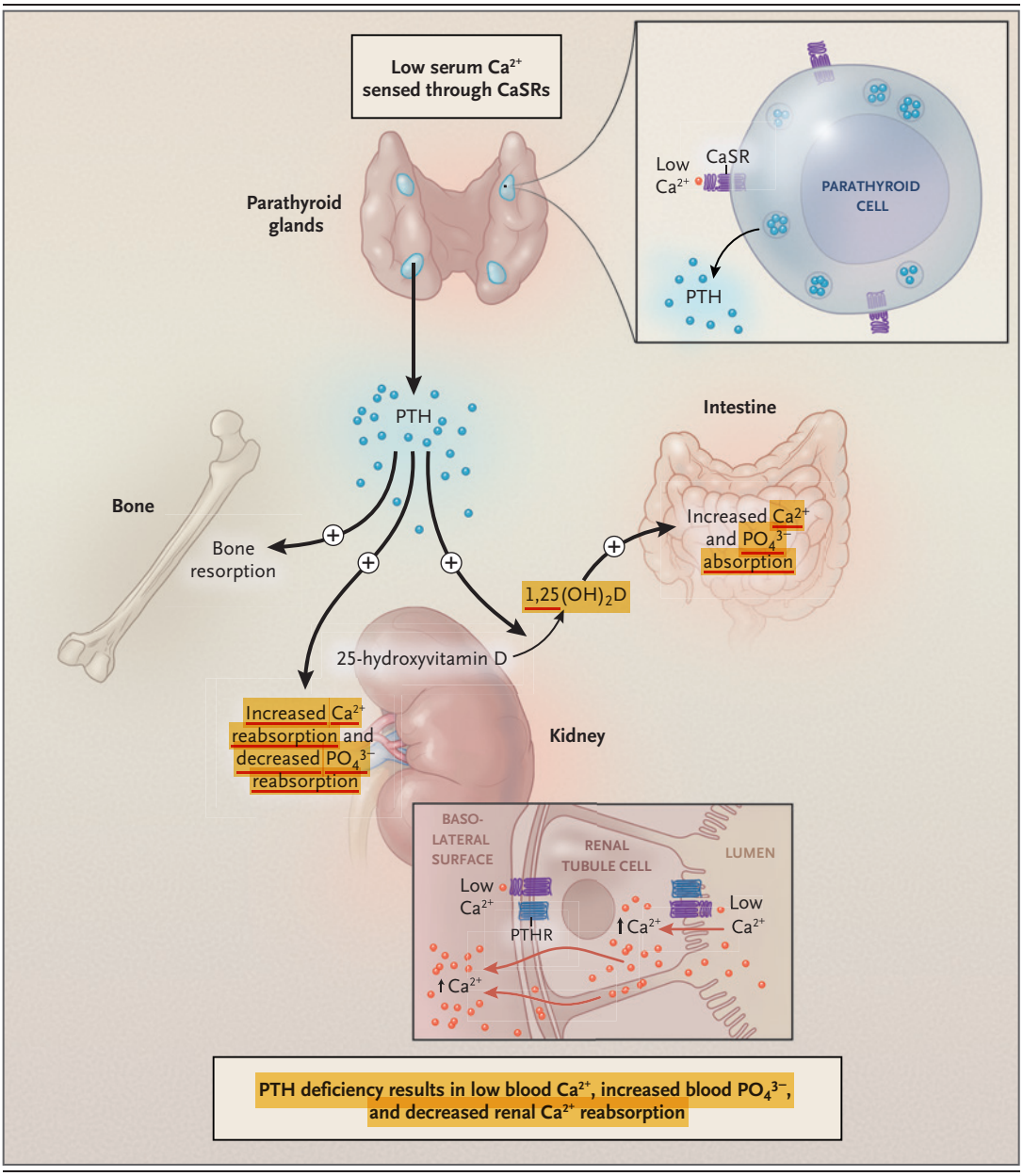
PREVENTION

Large epidemiologic studies have estimated that the overall incidence of hypoparathyroidism after anterior neck surgery is approximately 8%, with 75% of cases resolving within 6 months and the remaining 25% resulting in permanent hypoparathyroidism.[2,20] Postsurgical hypoparathyroidism is much less common when surgery is performed by experienced neck surgeons who perform at least 50 to 100 thyroidectomies or parathyroidectomies per year. At high-volume centers, hypoparathyroidism develops in less than 2% of patients undergoing these operations.[21] Additional predictors of permanent postsurgical hypoparathyroidism include extensive neck dissection, exploration on both sides of the neck, repeat neck surgery, a history of Graves' disease, an inability to visualize the parathyroid glands during surgery, a calcium level of less than 7.5 mg per deciliter (1.88 mmol per liter) 24 hours after surgery, and postoperative bleeding resulting in additional surgery.[21,22] After surgery, close monitoring of calcium and PTH levels is indicated in order to identify hypoparathyroidism before the development of severe, symptomatic hypocalcemia. Rarely, hypoparathyroidism can develop years after surgery.[23]

DIAGNOSIS AND EVALUATION

Hypoparathyroidism is suspected in patients with a low ionized or albumin-corrected blood calcium level, hyperphosphatemia, and an intact PTH level that is low or that is inappropriately in the normal range. When the blood calcium level is low, the intact PTH level would be expected to be elevated. In patients who have not undergone neck surgery, the differential diagnosis of hypoparathyroidism is broad and can be subdivided into disorders of parathyroid gland formation, parathyroid hormone secretion, and parathyroid gland destruction (Table S1 in the Supplementary Appendix).

Although genetic disorders typically become apparent in childhood, subtle manifestations of hypoparathyroidism may be missed, particularly if hypocalcemia is mild or intermittent. For example, the incidence of chromosome 22q11.2 deletion syndrome is 1 case per 3000 live births, and hypoparathyroidism of varying severity is present in approximately half the affected per-



sons.[24] Pathogenic variants that constitutively activate the CaSR cause autosomal dominant hypocalcemia type 1 (ADH1), which results in both decreased PTH secretion and decreased renal calcium reabsorption.[5] Autoimmune polyendocrinopathy candidiasis with ectodermal dystrophy (APECED) should be considered in patients with hypoparathyroidism who have chronic candidiasis or other autoimmune disorders.[25]

Syndromic and genetic disorders can often be diagnosed by means of a thorough history, physical examination, and laboratory assessment; however, some patients may have only minor characteristics of a particular syndrome. Genetic testing with the use of targeted gene analysis or multigene panels should be pursued, depending on cost and availability, particularly in patients in whom new variants are not seen in other family members.

CONVENTIONAL THERAPY FOR HYPOPARATHYROIDISM

Emergency Management

Emergency management of hypocalcemia-induced tetany and seizures is 10% calcium gluconate (93 mg of elemental calcium per 10 ml of solution) infused over a period of 10 to 15 minutes,

Figure 1 (facing page). Control of Mineral Homeostasis by Parathyroid Hormone and the Calcium-Sensing Receptor.

A decrease in the blood calcium level triggers a cascade of events, primarily mediated through the action of parathyroid hormone (PTH) and ionized calcium (Ca^{2+}) on the PTH receptor and the calcium-sensing receptor (CaSR), both of which are 7-transmembrane, G-protein–coupled receptors. At the parathyroid gland, both the rate and magnitude of change in the blood calcium level are detected by CaSRs. In response to a decreasing calcium level, PTH secretion is triggered (blue spheres).[4] PTH has direct mineral-regulating effects at the bone, where it promotes the release of calcium and phosphate (PO_4^{3-}) by means of bone resorption. At the kidney, it facilitates reabsorption of calcium (orange spheres) from the filtrate to the blood while concurrently inhibiting phosphate reabsorption from the filtrate, thus promoting phosphate excretion into the urine. PTH acts indirectly at the gut through the action of PTH-stimulated renal production of 1,25-dihydroxyvitamin D ($1,25[OH]_2D$) to increase calcium and phosphate absorption from the gut. Much of the fine-tuning of blood and urinary calcium and phosphate levels takes place at the kidney through the action of PTH, the CaSR,[5] and fibroblast growth factor 23 (FGF-23; not shown). Renal mineral homeostasis regulation is complex. A generic renal tubule cell is shown and highlights the fact that the PTH receptor and CaSR can be found on both the luminal (urine) and basolateral (blood) surface of cells. Their expression level and action vary along the nephron, depending on the function of the segment. The physiological response to a decrease in the blood calcium level (depicted in the bottom inset as low Ca^{2+} on the basolateral side and in the filtrate on the luminal side), is to promote the reabsorption of calcium from the filtrate by means of both paracellular and transcellular mechanisms (indicated by the orange arrows) to return the blood calcium level to normal. In the hypoparathyroid state, the entire cascade is perturbed, and PTH-mediated calcium and phosphate regulation is disrupted. The blood calcium level is decreased, urinary calcium excretion is increased, and the blood phosphate level is elevated. Decreased renal calcium reabsorption can manifest as an inappropriately normal urine calcium level or as an elevated urine calcium level in the context of a low blood calcium level.

often followed by a continuous infusion to prevent recurrent hypocalcemia while oral therapy is being initiated (Table 1). Calcium gluconate is preferred because it can be administered in a peripheral vein, whereas other preparations must be administered by means of a central venous catheter. Given the arrhythmogenic effects of acute calcium alterations, cardiac monitoring during calcium infusions is recommended.

Long-Term Management

In contrast to most hormone deficiencies, for which hormone replacement is the mainstay of therapy, hypoparathyroidism has been conventionally treated with high-dose vitamin D (cholecalciferol or ergocalciferol) and calcium supplements or with activated vitamin D and calcium supplements (Table 1). Large, randomized, controlled trials evaluating conventional management of hypoparathyroidism have been limited, and standard practice is based on case series, expert opinion, and consensus guidelines.[26] Calcium carbonate, which is 40% by weight elemental calcium, is given orally, is economical, and is widely available. Because an acidic environment is required for effective absorption of calcium carbonate,[27] alternatives that do not require a low gastric pH, such as calcium citrate, are recommended for persons taking acid-blocking therapy. Patients who are taking levothyroxine, which is poorly absorbed when taken with calcium, should be instructed to always take the medications separately or to consistently take them together.

Because PTH is needed for activation of renal 25-hydroxyvitamin D 1α-hydroxylase, vitamin D analogues that have already undergone 1α-hydroxylation (calcitriol and alfacalcidol) are generally preferred[28]; these have a relatively short half-life as compared with other vitamin D analogues, thus decreasing the risk of prolonged hypercalcemia if vitamin D intoxication occurs. However, high doses of cholecalciferol and ergocalciferol, which have a long half-life and were the mainstay of therapy before the availability of 1α-hydroxylated vitamin D analogues, may also be considered.[29] Although vitamin D intoxication is less likely with cholecalciferol and ergocalciferol than with calcitriol, when it occurs hypercalcemia is more sustained than with calcitriol or alfacalcidol intoxication. Because PTH is also involved in renal magnesium handling,[30] some patients (particularly those with autosomal dominant hypocalcemia) have hypomagnesemia and benefit from magnesium supplements.[5]

Dosage requirements are highly individualized, with some patients being easily treated with simple regimens and others having disease that is refractory to therapy, in rare cases leading to continuous calcium infusions. Conventional treatment does not address the lack of PTH-mediated renal calcium reabsorption or phosphate excretion. Even with close monitoring, patients may continue to have hyperphosphatemia, and hypercalciuria may develop. The combination of hyperphosphatemia and hypercalciuria increases the risk of renal calcification,

Table 1. Medications for the Treatment of Hypoparathyroidism.*

Medication	Formulation	Route	Administration in Adults	Comments
Calcium				
Calcium gluconate 10%	93 mg of elemental calcium per 10 ml of solution	Intravenous	Bolus: 10–20 ml over 10–15 min; continuous infusion: 1.25 mg of elemental calcium per kilogram of body weight per hour	9.3% elemental calcium; ECG monitoring recommended
Calcium chloride 10%	270 mg of elemental calcium per 10 ml of solution	Central venous catheter only	Bolus: 5–10 ml over 5–10 min	27% elemental calcium; ECG monitoring recommended
Calcium carbonate	Suspension: 100 mg of elemental calcium per 1 ml of solution; tablets and capsules: 160–600 mg of elemental calcium; chews: 500 mg of elemental calcium per chew; and Cal-EZ: 1000 mg of elemental calcium per packet	Oral	0.5–2 g of elemental calcium, divided into 2–4 doses per day	40% elemental calcium; ideally taken with meals for better absorption and to act as a phosphate binder
Calcium citrate	Tablets: 180–760 mg of elemental calcium	Oral	0.5–2 g of elemental calcium, divided into 2–4 doses per day	21% elemental calcium; ideally taken with meals for better absorption and to act as a phosphate binder
Calcium glubionate	115 mg elemental of calcium per 5 ml of solution	Oral	0.5–2 g of elemental calcium, divided into 2–4 doses per day	6.4% elemental calcium; ideally taken with meals
Magnesium				
Magnesium sulfate	492 mg of elemental magnesium per 1 ml of solution	Intravenous	Bolus: 1–2 g over 2–15 min; continuous infusion: 4–8 g (40–81 mg of elemental magnesium) over 24 hr	9.86% elemental magnesium; ECG monitoring recommended
Magnesium oxide	Tablets or capsules: 250–500 mg	Oral	250–1000 mg of elemental magnesium, divided into 2–4 doses per day	60% elemental magnesium
Vitamin D				
Ergocalciferol	Liquid: 8000 IU/ml; capsules: 50,000 IU	Oral	400–4000 IU/day with calcitriol†; 10,000–100,000 IU/day without calcitriol	Target 25-hydroxyvitamin D level: 20–60 ng/ml with calcitriol or >80 ng/ml without calcitriol
Cholecalciferol	Liquid: 400 IU/ml; capsules: 400–50,000 IU	Oral	400–4000 IU/day with calcitriol†; 10,000–100,000 IU/day without calcitriol	Target 25-hydroxyvitamin D level: 20–60 ng/ml with calcitriol or >80 ng/ml without calcitriol
Calcitriol	Liquid: 1 μg/ml; capsules: 0.25 and 0.5 μg	Oral or intravenous for liquid‡; oral for capsules	0.25–3 μg/day, divided into 2 doses per day	Onset of action, 1–2 days; offset of action, 2–3 days; half-life, 5–8 hr

Alfacalcidol	Liquid: 2 μg/ml; capsules: 0.25, 0.5, and 1 μg	Oral or intravenous for liquid‡; oral for capsules	0.25–3 μg/day	Onset and offset of action, within 3 days; half-life, 3–6 hr; not available in the United States
Human recombinant parathyroid hormone				
PTH 1–84§	Pen injector: 25, 50, 75, or 100 μg	Subcutaneous	Start with 50 μg/day; adjust by 25 μg every 4 wk; maximum dose, 100 μg/day	Fixed-dose pen; calcium and calcitriol supplementation may still be appropriate
PTH 1–34	Pen injector: 20 μg	Subcutaneous	NA	Not approved for treatment of hypoparathyroidism

* ECG denotes electrocardiogram, NA not applicable, and PTH parathyroid hormone.
† This dose is used as needed to maintain normal blood levels of vitamin D.
‡ Intravenous therapy is used in patients who are unable to take medications orally.
§ PTH 1–84 is the only medication that has been approved specifically for use in patients with hypoparathyroidism, and it has been approved for use only in adults.

which has been reported to affect more than one third of adults with predominantly acquired hypoparathyroidism[15] and a similar percentage of children with predominantly nonsurgical hypoparathyroidism.[31] Renal insufficiency is increased in patients with hypoparathyroidism,[15,31] particularly those with nonsurgical hypoparathyroidism.[12] Increased risk appears to correlate with higher blood calcium concentrations and a longer duration of relative hypercalcemia.[15,31] Given the risk of renal insufficiency due to nephrocalcinosis, it is recommended that blood calcium levels be targeted to the lower end of the normal range, in order to reduce hypercalciuria, and that urinary calcium levels be carefully monitored (Table 2).

PARATHYROID HORMONE THERAPY

Recombinant human PTH 1–84 has been approved for the treatment of hypoparathyroidism in both the United States and (conditionally) in Europe in adults who have disease that is refractory to conventional therapy, with the exception of patients who have autosomal dominant hypocalcemia, who were not included in clinical trials. Many studies have shown that hypocalcemia can be adequately managed in most patients by means of once-daily or twice-daily subcutaneous injections of teriparatide (PTH 1–34 fragment) or intact PTH (PTH 1–84).[34-38] In a 6-month, placebo-controlled trial, the use of PTH 1–84 also reduced blood phosphate levels,[39] which may be important in preventing ectopic calcifications. However, PTH 1–34 and PTH 1–84 therapies have both shown inconsistent effects on hypercalciuria, and long-term studies to determine whether PTH therapy reduces the development or progression of renal calcifications or renal insufficiency have been limited.

A recent open-label study showed that, despite a decrease in urinary calcium excretion and an increase in the estimated glomerular filtration rate, twice-daily PTH 1–34 therapy induced hypocitraturia, which is an established risk factor for renal calcification.[40] New or worsening nephrocalcinosis or nephrolithiasis, as assessed on imaging, developed in half the study participants over a mean of 37 months of treatment.[40] In a 6-year study, symptomatic nephrolithiasis developed in 3 of 33 participants who were taking PTH 1–84.[35]

Bone turnover is low in patients with hypoparathyroidism[8] and is stimulated by intermittent

Table 2. Monitoring and Therapeutic Targets.*

Measure	Frequency	Target	Comments
Blood			
Total calcium	Every 3–6 mo	At or slightly below lower limit of normal range (approximately 7.8–8.5 mg/dl)	Lowest level to avoid clinically significant neuromuscular symptoms without side effects; correct for albumin level or check ionized calcium level if indicated
Phosphate	Every 3–6 mo	Upper limit of age-specific normal range	Calcium supplements are taken with meals to decrease phosphate absorption; avoid excessive doses of calcitriol, which increases phosphate absorption
Total calcium × phosphate†	Every 3–6 mo	<55 mg^2/dl^2 (in adults)	Higher levels may increase risk of ectopic calcifications
Magnesium	Every 3–6 mo	Normal range	If level is low, consider magnesium supplementation
Creatinine	Every 3–6 mo	Normal range	For calculation of estimated GFR
25-hydroxyvitamin D	Every 6–12 mo	>20–30 ng/ml	Maintain higher level if cholecalciferol is being used to manage hypocalcemia
Urine			
Calcium	Every 6–12 mo	<4 mg/kg/day	24-hr collections are preferred; consider thiazide diuretics for substantial hypercalciuria
Creatinine	Every 6–12 mo	10–20 mg/kg/day in women; 15–25 mg/kg/day in men	Important to ensure adequate urine collection
Sodium	Every 6–12 mo	<220 mmol/day	24-hr sodium collection should be done concurrently with calcium assessment
Supersaturation or stone profile (e.g., citrate, oxalate, urate)	Every 6–12 mo as needed in patients with substantial hypercalciuria or renal calcifications	Normal range	Monitor for hypocitraturia while patient is taking PTH therapy; consider potassium citrate for hypocitraturia; consider low-oxalate diet for hyperoxaluria
Imaging			
Renal ultrasonography	Every 1–5 yr	NA	Evaluate for nephrocalcinosis and nephrolithiasis
Renal CT	Only if clinically indicated	NA	Consider CT in patients with acute nephrolithiasis
Bone densitometry	Only if clinically indicated	NA	Recommend monitoring in patients who have fragility fractures or are taking PTH therapy

* To convert values for blood calcium to millimoles per liter, multiply by 0.250. To convert values for 25-hydroxyvitamin D to nanomoles per liter, multiply by 2.496. To convert values for urinary calcium to millimoles per kilogram per day, multiply by 0.025. To convert values for urinary creatinine to millimoles per kilogram per day, multiply by 0.0088. CT denotes computed tomography, and GFR glomerular filtration rate.

† The calcium × phosphate product, as a risk factor for ectopic calcifications, has not been validated in patients with hypoparathyroidism. However, the summary statements and guidelines on which this table is based recommend being mindful of this measure.[22,32,33]

subcutaneous PTH therapy, with bone turnover often still elevated above the normal range several years into treatment.[34,35,41-43] PTH therapy has differential effects on skeletal compartments, with anabolic effects on trabecular bone and catabolic effects on cortical bone. Small case series involving patients who were treated with PTH 1–34 (for 18 months) or PTH 1–84 (for 8 years) have shown increased cancellous bone volume, trabecular number, and cortical porosity.[38,41] A report of a single patient with autosomal dominant hypocalcemia who was treated continuously with PTH 1–34 from the age of 6 years to the age of 20 years described skull thickening with diffuse sclerotic and lytic lesions, increased trabecular bone on bone biopsy, and decreased radial bone density.[43] However, other data suggest that these findings may be transient, with the skeleton becoming more euparathyroid in structure with continued therapy.[44]

Given the high bone turnover that is induced by PTH treatment, the discontinuation of PTH 1–34 therapy should be done gradually, with frequent monitoring and concomitant administration of higher than pre–PTH therapy doses of calcium and calcitriol to prevent severe hypocalcemia as the bone returns to a low-turnover state,[42] similar to the hungry bone syndrome

that is seen after parathyroidectomy in patients with hyperparathyroidism. Hypocalcemia has also been noted more frequently after the discontinuation of PTH 1–84 therapy than after the discontinuation of placebo.[36]

Studies of the effects of PTH 1–84 therapy on quality-of-life measures have shown varying results. Some open-label studies have suggested improvement in quality of life,[45] but a placebo-controlled trial showed no significant differences between PTH 1–84 therapy and placebo.[46]

Both PTH 1–34, which is approved for the treatment of osteoporosis, and PTH 1–84 carry a black-box warning of a risk of osteosarcoma. In contrast to the use of PTH 1–34 for osteoporosis, in which therapy is recommended to be stopped after 24 months, a maximum duration of therapy is not defined for PTH 1–84 in patients with hypoparathyroidism.

MONITORING

Frequent monitoring of blood calcium, phosphate, magnesium, and creatinine levels and of urinary calcium excretion is essential to avoid overtreatment or undertreatment (Table 2).[26] Blood calcium levels are targeted at or slightly below the lower limit of the normal range, to the extent possible, while being careful to avoid the neuromuscular symptoms of hypocalcemia. Maintenance of slightly low blood calcium levels is necessary to avoid hypercalciuria, defined by a 24-hour excretion of more than 4 mg of calcium per kilogram of body weight per day (>0.1 mmol per kilogram per day). In patients with obesity, the ideal body weight should be used to assess calcium excretion, and sex-specific normal ranges should be considered (<300 mg per day [<7.5 mmol per day] in men, and <250 mg per day [<6.2 mmol per day] in women). Because some patients may have other risk factors for renal calcification, such as hypocitraturia,[40] more-comprehensive urine studies may be warranted.

Periodic renal imaging to evaluate for nephrocalcinosis and nephrolithiasis may further guide therapy. Ultrasonography is preferred because it does not involve ionizing radiation and is more sensitive than computed tomography for the detection of early nephrocalcinosis.[47] Patients with long-standing hypoparathyroidism should undergo regular ophthalmologic and dental examinations. Patients with syndromic or autoimmune hypoparathyroidism also need to undergo continued monitoring for expected coexisting conditions (Table S1 in the Supplementary Appendix).

AREAS OF UNCERTAINTY

POSSIBLE RENOPROTECTIVE THERAPIES

Given that hypercalciuria with renal calcification is a major complication with conventional therapy, thiazide diuretics combined with a low-salt diet, which decrease urinary calcium excretion, may be considered as adjuvant therapy. Although this treatment has been shown to raise blood calcium levels in two small, uncontrolled studies involving patients with hypoparathyroidism,[48] the use of thiazide diuretics has not been systematically tested, and monitoring for hypokalemia is warranted. Although hypocitraturia has been reported in patients with hypoparathyroidism who have been treated with either conventional therapy or PTH,[40] the renoprotective benefit of potassium citrate treatment is unknown.

PHOSPHATE BINDERS

Research regarding the use of phosphate binders such as sevelamer hydrochloride and lanthanum carbonate in patients with hypoparathyroidism has been limited. Since calcium is an effective phosphate binder, taking calcium supplements in divided doses with meals may be a better approach to managing hyperphosphatemia.

DIET

Eating a diet rich in calcium is generally recommended, although studies comparing the effects of dietary calcium with those of calcium supplements on hypocalcemia or hypercalciuria in patients with hypoparathyroidism have been limited. Reducing the intake of dairy products may be prudent because they are also high in phosphorus, although strict phosphate restriction is not considered to be a mainstay of therapy. Maintaining adequate daily water intake and limiting dietary sodium may reduce the risk of renal calcifications, as has been shown in patients with idiopathic hypercalciuria.[49]

PREGNANCY

Management of hypoparathyroidism during pregnancy has not been systematically studied. Although data are limited to small case series, clinical experience supports the efficacy and safety of calcitriol therapy during pregnancy, with requirements varying over the course of the

pregnancy.[50] Hypocalcemia may promote preterm labor and put the neonate at risk for hyperparathyroidism. For this and other reasons, hypoparathyroidism during pregnancy should be considered a high-risk state.[50]

PHARMACOTHERAPY

More data are needed to inform long-term benefits and risks of PTH 1–84 therapy as compared with conventional therapy. Small, short-term, crossover studies have suggested that continuous subcutaneous PTH 1–34 infusions delivered by pump may be more physiologic than injections.[51] Long-acting PTH analogues,[52] PTH-related protein analogues,[53] PTH receptor modulators,[54] and antagonists of the CaSR (calcilytics)[55] are all in various stages of development; study is needed to assess their potential roles in practice.

GUIDELINES

The European Society of Endocrinology[32] and the First International Conference on the Management of Hypoparathyroidism[33] have published management guidelines. The American Thyroid Association published a statement on the diagnosis, prevention, and management of postoperative hypoparathyroidism.[22] The majority of the recommendations in these guidelines are based on expert opinion and small studies rather than on large, controlled trials. The recommendations in this review are generally consistent with these guidelines.

CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette has new-onset hypocalcemia consistent with hypoparathyroidism. Urgent treatment with intravenous calcium (calcium gluconate, if administered through a peripheral intravenous catheter) is appropriate. We would also promptly initiate oral calcium carbonate and calcitriol therapy in divided doses to minimize symptoms of hypocalcemia and to maintain an albumin-adjusted blood calcium level near the low end of the normal range and 24-hour urinary calcium excretion in the weight-adjusted normal range. If treatment with calcium and calcitriol was ineffective at controlling symptoms of hypocalcemia, we would consider treatment with PTH 1–84, as well as calcium and vitamin D supplementation as needed. The patient's strong family history of autoimmunity suggests an autoimmune cause of hypoparathyroidism and necessitates screening and surveillance for other autoimmune disease in this patient.

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