CLINICAL PRACTICE

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 author's clinical recommendations.*

A 58-year-old man is found on laboratory testing to have a serum calcium level of 6.0 mg per deciliter (1.5 mmol per liter) (normal range, 8.5 to 10.5 mg per deciliter [2.1 to 2.6 mmol per liter]), an albumin level of 3.9 g per deciliter, and a phosphorus level of 6.0 mg per deciliter (1.94 mmol per liter) (normal range, 2.5 to 4.5 mg per deciliter [0.81 to 1.45 mmol per liter]). His medical history is notable only for long-standing hearing difficulties. He reports no history of neck surgery and no throat tightness, muscle cramps, paresthesias, or seizures. His father and sister, who are both deceased, had kidney disease. On physical examination, both Chvostek's and Trousseau's signs are negative. His ionized calcium level is 0.75 mmol per liter (normal range, 1.10 to 1.32). How should his case be further evaluated and treated?

THE CLINICAL PROBLEM

Hypocalcemia, defined as low serum levels of albumin-corrected total calcium or of ionized calcium, is a common clinical occurrence and has many potential causes. Viewed broadly, hypocalcemia results from inadequate parathyroid hormone (PTH) secretion or receptor activation, an insufficient supply of vitamin D or activity of the vitamin D receptor, abnormal magnesium metabolism, or clinical situations in which multiple factors (e.g., pancreatitis, sepsis, and critical illness) play contributing roles. Hypocalcemia can present dramatically as tetany, seizures, altered mental status, refractory congestive heart failure, or stridor. The duration, severity, and rate of development of hypocalcemia determine the clinical presentation. Neuromuscular symptoms are typically the most prominent; these symptoms include muscle cramping, twitching, and spasms; circumoral and acral numbness and paresthesias; laryngospasm; bronchospasm; and even seizures. Other complications include premature cataracts, pseudotumor cerebri, and calcifications of the basal ganglia. Cardiac function may be affected, manifested by a prolonged QT interval corrected for heart rate (QTc) on electrocardiographic examination and, in rare cases, depressed systolic function and heart failure. Especially if the disturbance is chronic, patients with remarkably low levels of ionized calcium may be asymptomatic.

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STRATEGIES AND EVIDENCE

DIFFERENTIAL DIAGNOSIS

Hypoparathyroidism causes hypocalcemia because PTH secretion is inadequate to mobilize calcium from bone, reabsorb calcium from the distal nephron, and stimulate renal 1α-hydroxylase activity; as a result, insufficient 1,25-dihydroxyvitamin D (1,25[OH]$_2$ vitamin D) is generated for efficient intestinal absorption of calcium (Fig. 1). Hypoparathyroidism can be congenital or acquired[1-3] (Table 1).

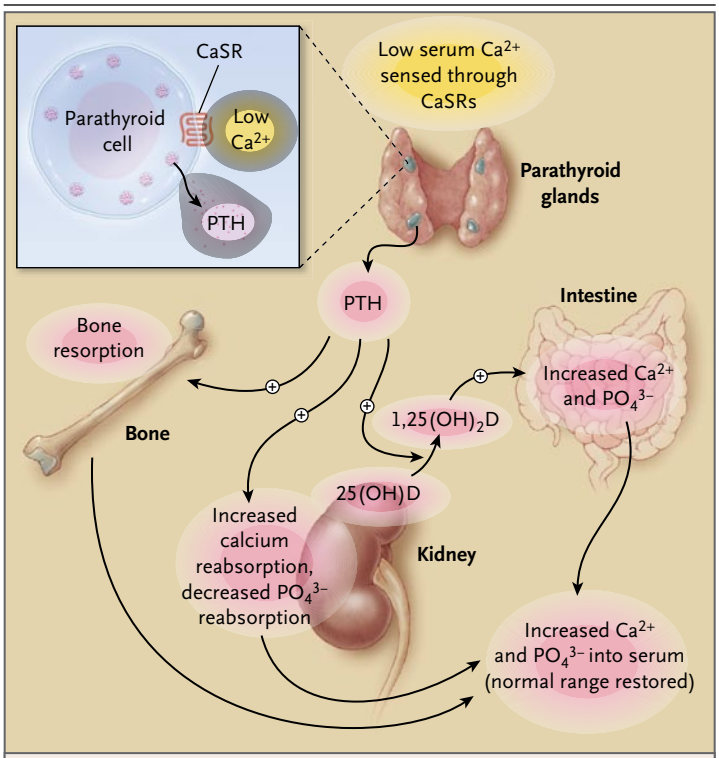

Figure 1. Control of Mineral Metabolism by Parathyroid Hormone.

Levels of serum ionized calcium (Ca^{2+}) are tightly controlled through the action of parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D ($1,25[OH]_2D$). Both the rate and magnitude of changes in the serum ionized Ca^{2+} concentration are detected by extracellular calcium-sensing receptors (CaSRs) expressed on parathyroid cells. When ionized Ca^{2+} levels decrease, the release of PTH secretion is triggered. Conversely, when ionized Ca^{2+} levels increase, PTH secretion is suppressed. PTH stimulates bone resorption, which delivers calcium and phosphorus (PO_4^{3-}) into the circulation. In the kidney, PTH stimulates renal reabsorption of calcium and promotes phosphate excretion. PTH also enhances the conversion of 25-hydroxyvitamin D (25[OH]D) to the active vitamin D metabolite $1,25(OH)_2D$, which increases the transepithelial transport of calcium and PO_4^{3-} through actions in intestinal cells. In concert, these steps restore ionized Ca^{2+} levels to the normal range, and, through the actions of PTH and other factors (e.g., fibroblast-derived growth factor 23) in the kidney, reset the level of serum PO_4^{3-} within the normal range. When the actions of PTH are reduced or lost, all subsequent steps in the maintenance of homeostasis are impaired, resulting in hypocalcemia, hyperphosphatemia, and hypercalciuria.

Acquired hypoparathyroidism is most commonly the result of inadvertent removal or irreversible damage to the glands, usually to their blood supply, during thyroidectomy, parathyroidectomy, or radical neck dissection. Definitions of permanent postsurgical hypoparathyroidism vary, but the definition is generally accepted to be insufficient PTH to maintain normocalcemia 6 months after surgery. Hypoparathyroidism is estimated to occur after approximately 0.5 to 6.6% of total thyroidectomies; the rates of this complication are even higher in some case series, whereas reported rates at endocrine surgical centers with high volumes are 0.9 to 1.6%.[25-28] The occurrence of hypoparathyroidism depends on the surgeon's experience, extent of thyroid resection and nodal dissection for cancer, and underlying thyroid disease, with the presence of substernal goiter, cancer, or Graves' disease increasing the risk. The risk is also greater if one or more parathyroid glands are not identified intraoperatively and if the procedure is a reoperation.

Parathyroid secretory reserve is ample, so considerable damage must occur before hypoparathyroidism develops. It is estimated that one normal gland is sufficient for maintaining PTH levels and serum calcium homeostasis. Immune-mediated destruction of the parathyroid glands can be either isolated or part of autoimmune polyendocrine syndrome type 1 (APS-1). Hypoparathyroidism may also be caused by accumulation in the parathyroid glands of iron (hemochromatosis or transfusion-dependent thalassemia)[5-7] or copper (Wilson's disease)[8] or (in rare cases) by iodine-131 therapy for thyroid diseases[29] or metastatic infiltration of the parathyroid glands by tumor[30] (Tables 1 and 2).

Magnesium depletion or excess may cause hypocalcemia by inducing functional hypoparathyroidism.[9,44-46] Magnesium is essential for PTH secretion and activation of the PTH receptor by ligand. In hypomagnesemia, PTH levels are inappropriately low or in the lower portion of the normal range, in the presence of usually mild hypocalcemia, because the parathyroid is unable to secrete sufficient hormone, and renal and skeletal responses to PTH are blunted. In rare instances, when magnesium is administered parenterally (e.g., in tocolytic therapy) or accumulates because of renal insufficiency and serum magnesium levels rise, PTH secretion is inhibited.[44,45] Magnesium, like calcium, can activate extracellular calcium-sensing receptors and suppress PTH release.[47] Once the magnesium status is corrected, the capacity to secrete PTH and respond to it resumes.

Genetic disorders must also be considered as a possible cause of hypocalcemia. The DiGeorge, or velocardiofacial, syndrome, due to microdele-

tions of chromosome 22q11.2, affects 1 in 4000 to 5000 live births.[39-41] Activating mutations in the extracellular calcium-sensing receptor are also frequently identified in patients with inherited hypoparathyroidism and are manifested as autosomal dominant hypocalcemia at any age (Tables 1 and 2).[10-13] Mutations in the pre-proPTH gene and in transcription factors that control parathyroid gland development are rare but shed light on basic developmental mechanisms.[2,15-18] Familial hypoparathyroidism due to dysgenesis of the parathyroid glands results from mutations in the transcription factors GCMB (glial cells missing B) or GCM2 (glial cells missing 2)[19-21] and GATA3[2,3,22,23] and possibly the transcription factor SOX3 (Sry-box 3) (Tables 1 and 2).[31] Other disorders that include hypoparathyroidism are the hypoparathyroidism, retardation, and dysmorphism syndrome and disorders due to mitochondrial-gene defects (Table 2).[2,3,36-38,42,43]

EVALUATION

Review of the patient's medical and family histories may suggest the cause of hypocalcemia. A history of neck surgery suggests that parathyroid function may have been compromised by the surgical procedure. A family history of hypocalcemia suggests a genetic cause (Table 2). The presence of other autoimmune endocrinopathies (e.g., adrenal insufficiency) or candidiasis prompts consideration of autoimmune polyendocrine syndrome type 1.[32-34] Immunodeficiency and other congenital defects point to the DiGeorge syndrome (Table 2).[39-41]

Physical examination should include an assessment of neuromuscular irritability by testing for Chvostek's and Trousseau's signs. Chvostek's sign is elicited by tapping the cheek (2 cm anterior to the earlobe below the zygomatic process) over the path of the facial nerve. A positive sign is ipsilateral twitching of the upper lip. Trousseau's sign is elicited by inflating a sphygmomanometer placed on the upper arm to a level above the systolic blood pressure for 3 minutes. A positive sign is the occurrence of a painful carpal spasm. The skin should be examined carefully for a neck scar (which suggests a postsurgical cause of hypocalcemia); for candidiasis and vitiligo (which are suggestive of APS-1); and for generalized bronzing and signs of liver disease (which are suggestive of hemochromatosis). Features such as growth failure, congenital anomalies, hearing loss, or retardation point to the possibility of genetic disease.

Laboratory testing should include measurements of serum total and ionized calcium, albumin, phosphorus, magnesium, creatinine, intact PTH, and 25-hydroxyvitamin D (25[OH] vitamin D) levels. Albumin-corrected total calcium is calculated as follows:

$$\text{Corrected total calcium} = \text{measured total calcium} + 0.8\ (4.0 - \text{serum albumin}),$$

where calcium is measured in milligrams per deciliter and albumin is measured in grams per deciliter. Hypoparathyroidism is diagnosed when the intact PTH level is normal or inappropriately low in a patient with subnormal serum albumin corrected total or ionized calcium values, after hypomagnesemia has been ruled out. Serum phosphorus levels are usually high or at the high end of the normal range. Patients with pseudohypoparathyroidism have a laboratory profile that resembles that in patients with hypoparathyroidism (i.e., low calcium and high phosphorus levels), but they have elevated PTH levels (Table 1). It may be difficult to rule out hypomagnesemia as the cause of or a contributor to hypocalcemia because the serum magnesium level may be normal, even when intracellular magnesium stores are reduced. Once magnesium depletion progresses, however, serum levels decrease to subnormal levels. In general, if the primary disturbance is magnesium depletion, serum calcium levels are only slightly decreased. Intact PTH is often detectable but inappropriately low.

Measurement of 25(OH) vitamin D levels is essential to rule out vitamin D deficiency as a contributor to or cause of hypocalcemia. In classic vitamin D deficiency, intact PTH levels are elevated, and serum phosphorus levels are low or at the low end of the normal range, in marked contrast to the high levels in hypoparathyroidism. Measurement of $1,25(OH)_2$ vitamin D levels is generally not necessary in the initial evaluation of patients with hypoparathyroidism.

Measurements of urinary calcium, magnesium, and creatinine in a 24-hour collection can also be helpful in the diagnosis of hypoparathyroidism. Low urinary calcium levels may be present in both severe hypocalcemia due to hypo-

Table 1. Pathophysiological Features of Disorders Considered in the Differential Diagnosis of Hypoparathyroidism.*

Mechanism and Disorder	Clinical Observations	Reference
Destruction or removal of parathyroid tissue, with inadequate secretory reserve remaining		
Postsurgical hypoparathyroidism	Most common form of hypoparathyroidism; can present years after surgery†	Winer et al.[4]
Autoimmune hypoparathyroidism	May be either isolated deficiency or combined with multiple endocrine deficiencies	
Radiation-induced destruction of parathyroid tissue	Very rare complication	
Metastatic infiltration of the parathyroid glands	Several documented cases due to a variety of underlying primary tumors, but generally rare site for metastases	
Deposition of heavy metals in parathyroid tissue	Occurs as a result of excess iron in ≥10% of patients with thalassemia, usually in second decade of life, when other end-organ complications (liver and heart disease, diabetes, hypogonadism, and hypothyroidism) are present, and correlates with extent of iron overload; less frequent complication of hemochromatosis and very rare complication of copper accumulation in Wilson's disease	Angelopoulos et al.,[5] Toumba et al.,[6] de Sèze et al.,[7] Carpenter et al.[8]
Reversible impairment of PTH secretion or PTH action with intact underlying secretory function		
Severe magnesium depletion	Associated with chronic conditions such as alcoholism, malnutrition, malabsorption, diarrhea, diabetes; drugs (e.g., diuretics, cisplatinum, aminoglycoside antibiotics, amphotericin B, and cyclosporine); metabolic acidosis; and renal disorders leading to magnesium wasting (chronic pyelonephritis, postobstructive nephropathy, renal tubular acidosis, primary renal magnesium wasting, and diuretic stage of acute tubular necrosis)	
Hypermagnesemia	May occur in patients receiving tocolytic therapy or in patients with chronic kidney disease receiving magnesium supplements, antacids, or laxatives	Tong and Rude[9]
Constitutively active CaSRs	Most commonly caused by mutations and rarely caused by acquired antibodies that stimulate the CaSR; appears to be among the most common causes of hypoparathyroidism	Winer et al.,[4] Brown,[10] Egbuna and Brown,[11] Yamamoto et al.,[12] Lienhardt et al.,[13] Kifor et al.[14]
Genetic disorders of PTH biosynthesis and parathyroid gland development		
PTH gene mutations	Responsible for isolated hypoparathyroidism	Arnold et al.,[15] Parkinson and Thakker,[16] Sunthornthepvarakul et al.,[17] Datta et al.[18]
Mutations or deletions in transcription factors and other regulators of the development of the parathyroid glands	May present as either isolated hypoparathyroidism (e.g., *GCMB* or *GCM2* mutations) or as part of complex genetic syndromes (e.g., *GATA3* mutations)	Ding et al.,[19] Baumber et al.,[20] Thomée et al.,[21] Van Esch et al.,[22] Ali et al.[23]
Mutations in mitochondrial DNA	May be manifested as hypoparathyroidism plus other metabolic disturbances and congenital anomalies	

Resistance to PTH action‡		
Pseudohypoparathyroidism		Bastepe[24]
Type 1a	Clinical features include AHO (round facies, mental retardation, frontal bossing, short stature, obesity, brachydactyly, ectopic ossifications), hypocalcemia, hyperphosphatemia, and elevated PTH levels; hypothyroidism develops in a majority of patients because of thyrotropin resistance and less frequently hypogonadism occurs as a result of gonadotropin resistance; autosomal dominant inheritance pattern with maternal transmission of the biochemical phenotype; blunted urinary cyclic AMP response to administration of PTH; a majority of patients have heterozygous inactivating mutations in the gene encoding the G_s-α subunit protein (the *GNAS* gene)	
Type 1b	No features of AHO, but same biochemical features as pseudohypoparathyroidism type 1a, including blunted urinary cyclic AMP response to administration of PTH; caused by selective resistance to PTH (not to other hormones) and by imprinting defects in *GNAS*	
Type 2	Less common than pseudohypoparathyroidism type 1a or 1b but with same biochemical profile; inherited or sporadic occurrence; cause of PTH resistance is unclear; patients have normal urinary cyclic AMP but no phosphaturic responses to PTH	

* AHO denotes Albright's hereditary osteodystrophy, CaSR extracellular calcium-sensing receptor, GCMB glial cells missing B, GCM2 glial cells missing 2, and PTH parathyroid hormone.
† The frequency of each of the diagnoses is difficult to establish because there are few large contemporary series of patients. The three most common causes appear to be postsurgical hypoparathyroidism, autoimmune polyendocrine syndrome type 1, and autosomal dominant hypocalcemia due to activating CaSR mutations.[4]
‡ Resistance lies in the pathway that couples receptor activation to the effector adenylate cyclase. These disorders must be considered in the initial evaluation of patients with hypocalcemia, especially if hyperphosphatemia is present. Once the intact PTH value is shown to be elevated and vitamin D deficiency or resistance is ruled out, the diagnosis of resistance to PTH action (not impaired PTH secretion) is established.

parathyroidism and in vitamin D deficiency. In patients with hypocalcemia due to activating mutations in the extracellular calcium-sensing receptor, the ratio of 24-hour urinary calcium to creatinine has been reported to be substantially higher than in patients with other types of hypoparathyroidism (mean value in one report, 0.362 vs. 0.093) and more like that in controls with normocalcemia (mean value, 0.331).[12]

If magnesium deficiency is detected, it is useful to measure the 24-hour urinary magnesium level before repletion is initiated. Elevated or even detectable urinary levels of magnesium suggest renal losses as the cause of magnesium depletion, since the kidney should conserve magnesium when body stores are depleted (Table 1).

Specialized testing (available in hospital or reference laboratories) may be warranted to establish the cause of hypoparathyroidism. This testing may include gene sequencing for the extracellular calcium-sensing receptor, GATA3, or the autoimmune regulator protein; microarray studies or fluorescence in situ hybridization to diagnose the DiGeorge syndrome; and other hormone measurements to diagnose autoimmune polyendocrine syndrome type 1. In many cases, referral to a pediatric or adult endocrinologist or geneticist is indicated.

TREATMENT AND CLINICAL MONITORING

The goals of therapy are to control symptoms while minimizing complications. The urgent care of patients with hypocalcemia should be guided by the nature and severity of the symptoms and the level of serum calcium.[46,48-51] Severe symptoms (e.g., seizures, laryngospasm, bronchospasm, cardiac failure, and altered mental status) warrant intravenous calcium therapy, even if the serum calcium level is only mildly reduced (e.g., 7.0 to 8.0 mg per deciliter [1.75 to 2.00 mmol per liter]). In such cases, the decrease in the serum calcium level may have precipitated the symptoms, and patients usually have immediate, substantial relief of symptoms with intravenous therapy (Table 3). Patients with congestive heart failure due to chronic hypocalcemia require additional medical treatment (e.g., supplemental oxygen and diuretics). Intravenous calcium therapy is also recommended in such patients, even though cardiac symptoms may resolve more slowly.

Intravenous calcium injections raise the level of serum calcium transiently; continuous infu-

Table 2. Genetic Syndromes and Other Inherited Forms of Hypoparathyroidism.*

Disorder	Responsible Locus or Gene	Inheritance	Pathogenic Mechanism	Comments	Reference
Familial hypocalcemia with hypercalciuria†	3q13,*CaSR*	Autosomal dominant	Heterozygous gain-of-function mutations in the *CaSR* that cause generally mild hypocalcemia and hypomagnesemia and hypercalciuria; mutant receptors cause a left-shifted set point for PTH secretion, defined as the extracellular calcium level required for half-maximal suppression of secretion; the altered set point causes inappropriately normal or low PTH levels even at low serum calcium levels	Phenotype caused by >40 mutations, mainly in extracellular and transmembrane domains of *CaSR*; Bartter's syndrome (salt wasting, hypokalemia, metabolic alkalosis, elevated renin and aldosterone levels) subtype V also described in a subgroup of patients; constitutive CaSR activation described in two patients with acquired antibodies that activate the *CaSR* along with other autoimmune conditions	Brown,[10] Egbuna and Brown,[11] Yamamoto et al.,[12] Lienhardt et al.,[13] Kifor et al.[14]
Familial isolated hypoparathyroidism	11p15, *pre-proPTH*	Autosomal recessive	Mutations in the signal peptide, disrupting PTH secretion, or in a donor-splice site of the PTH gene, leading to skipping of PTH exon 2, which contains the initiation codon and signal peptide	Homozygous mutations in the *pre-proPTH* gene cause very low or undetectable levels of PTH and symptomatic hypocalcemia	Parkinson and Thakker,[16] Sunthornthepvarakul et al.[17]
	11p15, *pre-proPTH*	Autosomal dominant	Point mutation in the signal sequence of *pre-proPTH* that prevents processing and translocation of PTH across endoplasmic reticulum and membrane for exocytosis	Mutant PTH is trapped within the endoplasmic reticulum inside cells; resulting stress in the endoplasmic reticulum is thought to predispose cells to undergo apoptosis	Arnold et al.,[15] Datta et al.[18]
	6p23-p24; *GCMB* or *GCM2*	Autosomal recessive	Large deletion of *GCMB* with loss-of-function or point mutations in the DNA-binding domain of *GCMB*, abolishing its transactivation capacity	*GCMB* is highly expressed in parathyroid tissue and controls embryologic development of parathyroid glands	Thakker,[2] Ding et al.,[19] Baumber et al.,[20] Thomée et al.[21]
X-linked hypoparathyroidism	Xq26-27	X-linked recessive	Deletion and insertion involving genetic material from chromosomes 2p25.3 and Xq27.1, causing a position effect on possible regulatory elements controlling *SOX3* transcription	Parathyroid agenesis; transcription factor SOX3 is thought to be expressed in the developing parathyroid glands	Bowl et al.[31]
APS-1‡	21q22.3 *AIRE*	Autosomal recessive	Loss-of-function mutations in *AIRE*, a zinc-finger transcription factor present in thymus and lymph nodes and critical for mediating central tolerance by the thymus; NALP5, an intracellular signaling molecule strongly expressed in the parathyroid, may be a specific parathyroid autoantigen in patients with APS-1; antibodies to NALP5 were identified in 49% of patients with APS-1 and hypoparathyroidism	Cases are concentrated in Finnish, Iranian Jewish, and Sardinian populations with >58 known mutations causing variable clinical presentations; classic triad is mucocutaneous candidiasis, adrenal insufficiency, and hypoparathyroidism (any two of these conditions are sufficient to establish the diagnosis); other features include hypogonadism, type 1 diabetes mellitus, hypothyroidism, vitiligo, alopecia, keratoconjunctivitis, hepatitis, pernicious anemia, and malabsorption‡; >80% of patients with APS-1 have hypoparathyroidism, which may be the sole endocrinopathy; presentation in childhood or adolescence is typical, but patients with only one disease manifestation should be followed long-term for the appearance of other signs of disease; occasional cases with autosomal dominant pattern of inheritance reported	Dittmar and Kahaly,[32] Eisenbarth and Gottlieb,[33] Perheentupa,[34] Alimohammadi et al.[35]

Syndrome of hypoparathyroidism, deafness, and renal anomalies	10p14-10-pter, *GATA3*	Autosomal dominant	Mutations or deletions that interfere with the ability of the transcription factor GATA3 to bind to DNA or interact with proteins that alter the expression of GATA3, a factor critical for parathyroid, kidney, and otic-vesicle development	Clinical features include hypoparathyroidism, bilateral sensorineural deafness (mild to profound), and renal anomalies or dysfunction	Thakker,[2] Goltzman and Cole,[3] Van Esch et al.,[22] Ali et al.[23]
Syndrome of hypoparathyroidism, growth and mental retardation, and dysmorphism	1q42-q43, *TBCE*	Autosomal recessive	Mutations in *TBCE* causing loss of function and probably altered microtubule assembly in affected tissues	Includes the Kenny–Caffey syndrome (short stature, osteosclerosis, cortical bone thickening, calcification of basal ganglia, ocular abnormalities, and hypoparathyroidism that is probably due to agenesis of the glands) and the Sanjad–Sakati syndrome (parathyroid aplasia, growth failure, ocular malformations, microencephaly, and retardation)	Thakker,[2] Parvari et al.,[36,37] Sanjad et al.[38]
DiGeorge, or velocardiofacial, syndrome	22q11.2, *TBX1*	Heterozygous deletions of chromosome 22q11.2 occurring mostly through new mutations	Loss of function of genes on chromosome 22q11, most notably *TBX1,* a transcription factor responsible for regulating expression of other transcription and growth factors important in development of thymus and parathyroid glands; parathyroid and thymic defects are caused by abnormal development in third and fourth branchial pouches	Wide phenotypic spectrum; may include conotruncal cardiac defects, parathyroid and thymic hypoplasia, neurocognitive problems, and palatal, renal, ocular, and skeletal anomalies; hypocalcemia (in 50–60% of patients) can be transient or permanent and can develop in adulthood; microarray analysis performed as an initial diagnostic screening test, with the deletion confirmed by FISH	Kobrynski and Sullivan,[39] Zweier et al.,[40] Goldmuntz[41]
Mitochondrial disorders with hypoparathyroidism	Mitochondrial gene defects	Maternal	Deletions of varying size, mutations, rearrangements, and duplications in the mitochondrial genome	Syndromes include the Kearns–Sayre syndrome (progressive external ophthalmoplegia, pigmentary retinopathy, heart block or cardiomyopathy, diabetes, and hypoparathyroidism); MELAS with diabetes and hypoparathyroidism; and MTPDS, a disorder of fatty-acid oxidation associated with peripheral neuropathy, retinopathy, acute fatty liver in pregnancy, and hypoparathyroidism	Thakker,[2] Cassandrini et al.,[42] Labarthe et al.[43]

* AIRE denotes autoimmune regulator protein, APS-1 autoimmune polyendocrine syndrome type 1, CaSR extracellular calcium-sensing receptor, FISH fluorescence in situ hybridization, GCMB glial cells missing B, MELAS mitochondrial encephalopathy, lactic acidosis, and strokelike episodes, MTPDS mitochondrial trifunctional protein deficiency syndrome, NALP5 NACHT leucine-rich-repeat protein 5, pre-proPTH pre-proparathyroid hormone, PTH parathyroid hormone, SOX3 Sry-box 3, TBCE tubulin chaperone E, and TBX1 T-box transcription factor 1.

† Cases that include Bartter's syndrome are caused by certain activating *CaSR* mutations (K29E, L125P, C131W, and A843E). Data are from Egbuna and Brown.[11] These mutant CaSRs are thought to inhibit the activity of a renal outer medullary potassium channel responsible for maintaining the transepithelial voltage gradient in the loop of Henle.

‡ Manifestations in a large Finnish cohort of patients included candidiasis (median age at onset, 5.4 years [range, 0.2 to 31.0]), hypoparathyroidism (6 years [1.6–43.0]), and adrenal insufficiency (10 years [3.5 to 41.0]); data are from Perheentupa.[34]

Table 3. Treatment of Hypoparathyroidism and Monitoring.

Agent	Formulation and Dose	Comments	References
For short-term management			
Calcium gluconate	1 g of calcium gluconate (93 mg of elemental calcium); infuse 1 or 2 g slowly, each over a period of 10 min, with electrocardiographic and clinical monitoring of the patient; this initial dose will increase the serum calcium level for only 2 or 3 hr, so it should be followed by a slow infusion of calcium; 10 g of calcium gluconate in 1 liter of 5% dextrose in water, infused at a rate of 1–3 mg/kg of body weight/hr in adults	Calcium-containing solutions can be irritating to surrounding tissues if extravasated, so a central venous catheter is preferred; therapy should be individualized and guided by frequent measurements of serum ionized calcium levels	Cooper and Gottoes,[46] Tohme and Bilezikian,[49] Brickman,[50] Rude[51]
For long-term management			
Calcium salts*			
Calcium carbonate	40% elemental calcium by weight; begin with 500–1000 mg of elemental calcium (three times per day) and adjust the dose to control symptoms and achieve the targeted calcium level; at least 1–2 g of elemental calcium (three times daily) generally required and more frequent dosing sometimes needed	Constipation is a common side effect; calcium carbonate is best absorbed with meals and with acid present in the stomach	
(Titralac)	420-mg tablet (168 mg of elemental calcium), 750-mg tablet (300 mg)		
(Os-Cal)	650-mg tablet (260 mg of elemental calcium), 1.25-g tablet (500 mg)		
(Tums)	500-mg tablet (200 mg of elemental calcium), 750-mg tablet (300 mg), 1000-mg tablet (400 mg), 1.2-g tablet (480 mg)		
(Caltrate)	1.5-g tablet (600 mg of elemental calcium)		
Calcium citrate	21% elemental calcium by weight	Recommended in patients who have achlorhydria or who are taking a proton-pump inhibitor, in order to achieve sufficient absorption of calcium	
(Citracal)	950-mg tablet (200 mg of elemental calcium)		

Vitamin D metabolites†			
Vitamin D_2 (ergocalciferol) or vitamin D_3 (cholecalciferol)	25,000–100,000 IU once daily; time to onset of action, 10–14 days; time to offset of action, 14–75 days	Vitamin D_3 is more potent than D_2 but may be more difficult to obtain at the doses needed. Because of the long half-life of vitamin D_2 and D_3, dosing can be adjusted and serum levels of calcium, albumin, phosphorus, and creatinine determined every 4 weeks, once symptoms have been controlled.	Cooper and Gottoes,[46] Tohme and Bilezikian,[49] Brickman,[50] Rude,[51] Okano et al.,[52] Halabe et al.[53]
1,25-dihydroxyvitamin D_3 (calcitriol)	0.25–1.0 μg once or twice daily; time to onset of action, 1–2 days; time to offset of action, 2–3 days	Most active metabolite of vitamin D at the vitamin D receptor in vivo	
1α-hydroxyvitamin D_3 (alfacalcidiol)	0.5–3.0 μg (occasionally up to 5.0 μg) daily; time to onset of action, 1–2 days; time to offset of action, 5–7 days	This metabolite is rapidly converted to 1,25-dihydroxyvitamin D_3 in vivo; its duration of action closely resembles that of 1,25-dihydroxyvitamin D_3	
Dihydrotachysterol	0.2–1.0 mg once daily; time to onset of action, 4–7 days; time to offset of action, 7–21 days		
Thiazide diuretics		Added to prevent or control hypercalciuria; should be combined with a low-salt diet (80–100 mmol of sodium per day) to promote calcium retention; doses are increased as tolerated; adverse events include hypokalemia and hyponatremia	Porter et al.[54]
Hydrochlorothiazide	25–100 mg per day	Doses at high end of these ranges are usually needed to achieve substantial lowering of urinary calcium	
Chlorthalidone	25–100 mg per day		
Amiloride and hydrochlorothiazide (Moduretic)	50 mg of hydrochlorothiazide combined with 5 mg of amiloride once daily	Potassium-sparing diuretics may be used to prevent hypokalemia	

* The list of calcium preparations is not comprehensive. Of the calcium preparations available, only the carbonate and citrate salts contain sufficient elemental calcium (per tablet) for the efficient treatment of most patients with hypoparathyroidism. Other preparations may be used in patients who cannot tolerate citrate and carbonate salts. The percentage of elemental calcium is lower in these other preparations: calcium lactate (13%), calcium gluconate (9%), and calcium glubionate (6.6%); thus, larger numbers of tablets must be given.

† Vitamin D toxicity is an important concern and may occur at any time. Manifestations may include altered mental status, fatigue, thirst, dehydration, reduced renal function, nephrolithiasis, and constipation. Treatment involves discontinuation of the vitamin D preparation and the calcium salt. Depending on the severity, and especially if the toxic effects are from vitamin D metabolites with long half-lives, intravenous saline hydration and possibly oral glucocorticoids may be warranted to antagonize vitamin D action and more rapidly restore normocalcemia. Levels of 25-hydroxyvitamin D should be monitored, even in patients receiving calcitrol and alfacalcidiol to prevent vitamin D insufficiency. The target 25-hydroxyvitamin D level is 30 ng/ml or more.

sions should follow to fully control symptoms and achieve safe and stable ionized calcium levels, usually above 1.0 mmol per liter. In the short term, the serum ionized calcium level should be measured frequently in order to monitor therapy (e.g., every 1 to 2 hours initially, while the infusion rate is being adjusted and until the patient's condition has stabilized, and then every 4 to 6 hours). The recurrence of symptoms caused by hypocalcemia may indicate the need to increase the infusion rate and should be correlated with a simultaneous ionized calcium value to assess the progress of treatment. Oral calcium and vitamin D therapy should be initiated as soon as practical (Table 3). Intravenous infusions are generally tapered slowly (over a period of 24 to 48 hours or longer) while oral therapy is adjusted. Patients with low calcium levels (e.g., total calcium, <7.0 mg per deciliter [<1.75 mmol per liter]) but minimal symptoms or none can often be treated as outpatients, with prompt initiation of oral calcium and vitamin D supplementation (preferably with calcitriol, because of its rapid onset of action) and close (daily) follow-up (Table 3). However, it is common in many institutions for patients with dramatically low serum calcium levels (even without symptoms) to be admitted for observation while treatment and a diagnostic workup are initiated. Oral therapy is appropriate in patients with mildly reduced serum total calcium levels (7.5 to 8.0 mg per deciliter [1.87 to 2.00 mmol per liter]) who have symptoms, even if they are nonspecific ones (e.g., fatigue, anxiety, and reduced well-being) because these symptoms may improve with treatment.

Vitamin D metabolites and analogues are essential to the management of hypoparathyroidism (Table 3).[46,48-53] The key complication to avoid is vitamin D intoxication (hypercalcemia and hypercalciuria) with its adverse effects on the renal and central nervous systems. Calcitriol is preferred (over vitamin D_2 or D_3) because of its potency and rapid onset and offset of action (Table 3). Thiazide diuretics can be used to reduce (or prevent) hypercalciuria caused by calcium and vitamin D therapy.[54] Once the 24-hour urinary calcium level approaches 250 mg, a thiazide diuretic combined with a low-salt diet can be added. Hyperphosphatemia may be addressed by minimizing the patient's dietary intake of phosphate (e.g., in meats, eggs, dairy products, and cola beverages) and, if needed, with phosphate binders to control or prevent an unacceptable calcium–phosphate product.

Levels of serum calcium, phosphorus, and creatinine should be measured weekly to monthly during initial dose adjustments, with twice-yearly measurements once the regimen has been stabilized. Urinary calcium and creatinine levels are measured twice yearly to detect any renal toxic effects of hypercalciuria. The goals of therapy are symptom control, a serum albumin-corrected total calcium level at the lower end of the normal range (approximately 8.0 to 8.5 mg per deciliter [2.00 to 2.12 mmol per liter]), a 24-hour urinary calcium level well below 300 mg, and a calcium–phosphate product below 55. Higher products can lead to precipitation of calcium–phosphate salts in soft tissues (e.g., kidney, lens, and basal ganglia). Annual slit-lamp and ophthalmoscopic examinations are recommended to monitor for the development of cataracts in all patients. The kidney is especially vulnerable in patients with hypoparathyroidism because the filtered load of calcium increases directly with increases in the serum calcium level. In the absence of PTH to promote renal calcium reabsorption, the additional calcium absorbed must be excreted through the kidneys.

There are no available data from clinical trials to show that complications of chronic hypocalcemia are preventable with aggressive therapy or that patients with mildly abnormal biochemical findings derive benefits from therapy. Clinical experience, however, indicates that patients with serum calcium levels near the lower end of the normal range tend to feel better, with less tetany, muscle cramps, and fatigue, than those with mild hypocalcemia who are not treated.

AREAS OF UNCERTAINTY

Hypoparathyroidism is one of the few endocrinopathies for which hormone-replacement therapy is not readily available. Only a few small, randomized trials have assessed the use of injectable human PTH (1–34) (Bachem California) in patients with this condition.[4,55] In a 3-year trial comparing PTH (1–34) with calcitriol, both given every 12 hours with supplemental calcium, both treat-

ments maintained the serum calcium level within or slightly below the normal range (7.6 to 8.8 mg per deciliter [1.9 to 2.2 mmol per liter]),[4] but the use of PTH resulted in less urinary calcium excretion. Although PTH significantly increased biochemical markers of bone turnover (as compared with no significant change with calcitriol), there were no differences in bone mineral density between the groups.[4] Creatinine clearances did not differ significantly between the groups, and they were stable in both groups during the study. PTH (1–34) is not approved by the Food and Drug Administration for this indication.

Limited data suggest that the quality of life may be compromised in patients with hypoparathyroidism despite treatment to optimize their biochemical values. In one study involving 25 women at a university center who were treated with vitamin D and calcium for postsurgical hypoparathyroidism, scores for somatization, depression, anxiety, and phobic anxiety were significantly higher than among age- and sex-matched controls with intact parathyroid function after thyroidectomy.[5,6] The effect of PTH replacement on quality-of-life measures is not known.

Whereas most patients with mutations in the extracellular calcium-sensing receptor have mild hypocalcemia for which no treatment is required,[10,11] some have severe, symptomatic hypocalcemia necessitating therapy. Because treatment with calcium and vitamin D in these patients may exacerbate baseline hypercalciuria and result in nephrocalcinosis and renal insufficiency, PTH therapy may warrant particular consideration in these patients. Several patients have been treated successfully with PTH therapy, averting hypercalciuria and reduced renal function.[4] More data, however, are needed before its use can be recommended in practice. In the future, drugs that antagonize the extracellular calcium-sensing receptor (i.e., calcilytic agents), which are in development, might be used to stimulate endogenous PTH in such patients.

GUIDELINES

There are no formal guidelines for the management of hypoparathyroidism.

CONCLUSIONS AND RECOMMENDATIONS

The initial evaluation of a patient with hypocalcemia should include a detailed family history (which may suggest a genetic cause) and relevant medical history (particularly regarding neck surgery and autoimmune disease). Laboratory testing should include measurements of serum total and ionized calcium, albumin, phosphorus, magnesium, and intact PTH levels. If the patient has severe symptoms, therapy with intravenous calcium should be initiated immediately, and the diagnosis pursued after the patient's condition has been stabilized. In the patient described in the vignette, the hearing deficits and family history of renal disease suggest the diagnosis of the syndrome of hypoparathyroidism, deafness, and renal anomalies. The expectation is that the intact PTH level would be detectable but low. Given the absence of symptoms in this patient, outpatient treatment with calcium carbonate three times daily and calcitriol once or twice daily would be appropriate, with adjustment as needed to maintain a target level of albumin-corrected serum calcium at the lower end of the normal range (approximately 8.0 to 8.5 mg per deciliter [2.00 to 2.12 mmol per liter]), a 24-hour urinary calcium level well below 300 mg, and a calcium–phosphate product below 55.

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An audio version of this article is available at www.nejm.org.

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