Presentation of Hypoparathyroidism: Etiologies and Clinical Features

Dolores M. Shoback[1], John P. Bilezikian[2], Aline G. Costa[3], David Dempster[4], Henning Dralle[5], Aliya A. Khan[6], Munro Peacock[7], Marco Raffaelli[8], Barbara C. Silva[9], Rajesh V. Thakker[10], Tamara Vokes[11], Roger Bouillon[12]

[1]Endocrine Research Unit, San Francisco Department of Veterans Affairs Medical Center, University of California, San Francisco; [2]Department of Medicine, Division of Endocrinology, Metabolic Bone Diseases Unit, College of Physicians and Surgeons, Columbia University, NY; [3]Department of Medicine, Division of Endocrinology, Metabolic Bone Diseases Unit, College of Physicians and Surgeons, Columbia University, NY, and Department of Medicine, Division of Endocrinology, São Paulo Federal University, São Paulo, Brazil; [4]Department of Pathology and Cell Biology, College of Physicians and Surgeons of Columbia University, NY, NY and Regional Bone Center, Helen Hayes Hospital, W Haverstraw, NY; [5]Department of General, Visceral and Vascular Surgery, University Hospital, Medical Faculty, Martin-Luther-University Halle-Wittenberg, Halle/Saale, Germany; [6]McMaster University Calcium Disorders Clinic, Hamilton, Canada; [7]Department of Medicine, IN University School of Medicine, Indianapolis, IN; [8]U.O. di Chirurgica Endocrina e Metabolica, Policlinico A. Gemelli, Università Cattolica del Sacro Cuore, Rome, Italy; [9]Department of Medicine of UNI-BH and Division of Endocrinology of Santa Casa de Belo Horizonte, Brazil; [10]Academic Endocrine Unit, University of Oxford, O.C.D.E.M, Churchill Hospital, Headington, Oxford, OX3 7LJ, UK; [11]Section of Endocrinology, Department of Medicine, University of Chicago, Chicago, IL; [12]Clinic and laboratory of experimental endocrinology, Gasthuisberg, KU Leuven, 3000 Leuven, Belgium *Report #3 from the First International Conference on "The Diagnosis, Management and Treatment of Hypoparathyroidism" held in Florence, Italy May 7–9, 2015* Date of revision 1: December 29, 2015 Date of revision 2: January 28, 2016

Context: Understanding the etiology, diagnosis, and symptoms may help to improve quality of life and long-term disease outcomes. This paper summarizes the results of the findings and recommendations of the Working Group on Presentation of Hypoparathyroidism.

Evidence acquisition: Experts convened in Florence, Italy, in May, 2015, and evaluated the literature and recent data on presentation and long-term outcomes of patients with hypoparathyroidism.

Evidence synthesis: The most frequent etiology is surgical removal or loss of viability of parathyroid glands. Despite precautions and expertise, about 20–30% of patients develop transient and 1–7% permanent postsurgical hypoparathyroidism after total thyroidectomy. Autoimmune destruction is the main reason for non-surgical hypoparathyroidism. Severe magnesium deficiency is an uncommon but correctable cause of hypoparathyroidism. Several genetic etiologies can result in loss of parathyroid function or action causing isolated hypoparathyroidism or a complex syndrome with other symptoms apart from those of hypoparathyroidism or pseudohypoparathyroidism. Neuromuscular signs or symptoms due to hypocalcemia are the main characteristics of the disease. Hyperphosphatemia can contribute to major long-term complications such as ectopic calcifications in the kidney, brain, eye or vasculature. Bone turnover is decreased, and bone mass is increased. Reduced quality of life and higher risks of renal stones, renal calcifications and renal failure are seen. The risk of seizures and silent or symptomatic calcifications of basal ganglia is also increased.

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Abbreviations:

Conclusions: Increased awareness of the etiology and presentation of the disease and new research efforts addressing specific questions formulated during the meeting should improve diagnosis, care, and long-term outcomes for patients.

Parathyroid hormone (PTH) is a major regulator of calcium and phosphate homeostasis. In bone and kidney, the actions of PTH are direct, whereas in the gastrointestinal (GI) tract, they are indirect via regulation of renal 1,25-dihydroxyvitamin D [1,25 $(OH)_2$ D] production. A negative sigmoidal relationship between the serum calcium (Ca^{2+}) concentration and PTH secretion is mediated via the parathyroid calcium-sensing receptor (CaSR). In contrast, serum phosphate does not directly regulate PTH secretion. The inappropriately low or frankly low PTH levels in relation to serum calcium concentration, characteristic of hypoparathyroidism, lead to decreased renal tubular reabsorption of calcium (TmCa) and simultaneously, to increased renal tubular reabsorption of phosphate (TmP). Thus, the main biochemical abnormalities of hypoparathyroidism are hypocalcemia and hyperphosphatemia. Hypocalcemia gives rise to most of the neuromuscular symptoms and signs of hypoparathyroidism, while hyperphosphatemia contributes importantly to ectopic mineralization in soft tissues (vasculature, brain, kidneys, and other organs).

Magnesium has a complex role in controlling PTH secretion and action. Magnesium is essential for a number of metabolic pathways and cellular functions and is an essential cofactor in enzymatic reactions. Serum ionized magnesium is tightly regulated. Renal magnesium reabsorption and 90% of the magnesium absorption in the bowel occur via a passive paracellular route. Transcellular absorption in the bowel and kidney is an active process via the transient receptor potential melastatin subtype 6 (TRPM6) channels. Magnesium activates the CaSR so hypermagnesemia decreases PTH synthesis and secretion. Mild hypomagnesemia stimulates PTH secretion. In contrast, severe hypomagnesemia decreases PTH secretion. This paradoxical block of PTH secretion is believed to be due to the effect of intracellular magnesium depletion on the alpha subunits of the G-proteins associated with the CaSR, resulting in decreased PTH secretion. Hypomagnesemia also results in target tissue resistance to the effects of PTH, in particular, in the renal tubules and in bone.

The full clinical presentation of hypoparathyroidism (symptoms, signs, and complications) is the direct result of destruction or dysfunction of the parathyroid gland and in particular the deficient secretion of PTH resulting in absent signaling in classic target tissues (bone and kidney) as well as other PTH receptor-expressing tissues. Hypoparathyroidism is thus a disease or syndrome due to (transient or permanent) lack of PTH or PTH signaling and can be diagnosed by the combination of low serum ionized or albumin-corrected calcium concentration and low or undetectable PTH. In contrast in pseudohypoparathyroidism (PHP), due to resistance to the hormone's actions, there is a combination of low serum calcium and high serum PTH levels. Over the lifetime of an individual, hypoparathyroidism can involve nearly every organ system in the body. Standard management to prevent hypocalcemia includes oral calcium supplements, calcitriol, or other active vitamin D analogues. Such chronic treatment can alleviate symptoms but may, however, produce a number of adverse effects that increase the burden of the disease. Therefore, along with the careful titration of medication and biochemical monitoring for disease control that hypoparathyroidism requires, the treating clinician must periodically assess renal, ocular, neurologic, neuromuscular, behavioral and skeletal parameters to avoid the complications of this chronic disorder and preserve quality of life (QOL) (QoL) for the patient.

The present manuscript focuses on updated information on the etiology and clinical presentation of hypoparathyroidism, whether isolated or part of more complex syndromes, and new data on the effects of chronic hypoparathyroidism on skeletal mass, microarchitecture, and remodeling. Other aspects of the disease as well as clinical management recommendations are discussed in two accompanying manuscripts in this issue of the *Journal* (one on Epidemiology and Diagnosis, the other on Management). Specialized topics such as management of hypoparathyroidism in pregnancy and lactation and the effects of the disease and its management in children and particularly on growth and development, while very important, are not discussed here but are covered in several excellent reviews (1–4). As there remain a large number of outstanding questions, the authors also present a number of research topics that need to be addressed to improve further the diagnosis, treatment, and prognosis of this disease.

I. CLINICAL FEATURES OF HYPOPARATHYROIDISM

Hypocalcemia causes well-known signs and symptoms because a low extracellular ionized calcium concentration ($[Ca^{2+}]$) can have a profound impact on a large number of tissues and organ systems including the brain, muscles, heart, and kidneys. The rapid onset of hypocalcemia in the postsurgical setting can present dramatically and in a manner that demands immediate and aggressive intervention. Alternatively, especially if the pace of development of the

condition is gradual, patients with hypocalcemia due to chronic hypoparathyroidism can be nearly asymptomatic, despite profound biochemical disturbances. Hyperphosphatemia is another consequence of hypoparathyroidism. It is asymptomatic and is responsible, over a much longer time frame, for ectopic mineralization and clinical consequences in soft tissues of the vascular, nervous, renal and other organs that can impair their function permanently.

General signs and symptoms

Most signs and symptoms of hypoparathyroidism are due to hypocalcemia, as low serum ionized [Ca^{2+}] can alter neurologic, cognitive, muscular, and cardiac function (5–7). Sometimes, this occurs in a highly insidious manner. Chronic hyperphosphatemia, mainly in the setting of treatment for the disease with oral calcium supplements, calcitriol, or other active vitamin D analogues, contributes to the ectopic calcifications noted above and the clinical consequences of renal stones and nephrocalcinosis. These ectopic calcifications are classically believed to be due to the chronically elevated phosphate levels and high calcium X phosphate product, resulting from the disease itself and from long-term treatment with activated vitamin D and calcium. High serum phosphate may also activate the inorganic phosphate transporter *pit1* (SLC20A1) and result in the expression of osteogenic molecules in the caudate nucleus and gray matter as mechanisms explaining calcifications in basal ganglia (8). Many patients with hypoparathyroidism also have chronically low serum magnesium levels. Serum magnesium should be evaluated and addressed if necessary in these patients since the signs and symptoms of hypocalcemia can be aggravated by concomitant magnesium deficiency.

Neurologic, muscular, psychiatric, cardiovascular, ophthalmologic, dermatologic, GI, and dental signs and symptoms are detailed in Table 1 and are not further discussed in this manuscript. More details can be found in recent reviews (5–10). Renal and skeletal manifestations and effects on QoL of hypoparathyroidism, both at baseline and due to treatment, are discussed in separate sections below.

Skeletal manifestations of hypoparathyroidism in patients on chronic treatment

Bone mass, microarchitecture, and turnover

Patients with hypoparathyroidism have bone mineral areal densities (BMDs) as measured by dual energy x-ray absorptiometry (DXA) that are greater than age- and sex-matched controls (11–15). Details of BMD Z- and T-scores obtained in 4 selected studies in adults are summarized in Supplemental Table 2. The increase in Z- and in T-scores usually approaches or exceeds 1 at most sites that include both cortical and trabecular bone, with the highest scores observed at the lumbar spine (LS) in adults as well as in children and adolescents. As an example, in 33 subjects with hypoparathyroidism, BMD Z-scores were +2.2 at the LS, +1.1 at the total hip (TH), +1.3 at the femoral neck (FN), and +0.7 at the 1/3 distal radius. BMD was positively correlated with the duration of hypoparathyroidism (12). Other reports essentially come to the same conclusion (Supplemental Table 2).

Trabecular bone score (TBS), a textural index that evaluates pixel gray-level variations derived from the LS DXA image, provides an indirect index of trabecular microarchitecture. TBS was found to be normal in subjects with hypoparathyroidism (16) (see Supplemental Table 2).

Advanced imaging has been used to assess bone in patients with hypoparathyroidism. Peripheral quantitative computed tomography (CT) (pQCT) of the radius was done in a small study of 9 women with hypoparathyroidism, comparing them to 36 women with primary hyperparathyroidism and 100 age-, gender-, and body size-matched normal controls. Trabecular volumetric (v) BMD was greater in the trabecular-enriched 4% distal radius, and cortical vBMD was higher at the cortical site (20% of the midradius), as compared to normal controls and hyperparathyroid women (11). Cortical area and cortical thickness were also increased in hypoparathyroid subjects. In addition, high-resolution (HR) pQCT of the radius and tibia revealed a consistent increase in cortical vBMD in men and women with hypoparathyroidism, as well as decreased cortical porosity at the radius and tibia in women and at the tibia in men (17). There was, however, no significant difference in estimated bone strength between hypoparathyroid and normal controls. Additional changes in HRpQCT parameters are shown in Supplemental Table 2.

The low bone turnover state of hypoparathyroidism is reflected in dynamic histomorphometry parameters and described below and in Supplemental Table 2. This feature is also reflected, but not to the same extent, by bone turnover markers (BTMs). BTMs are indeed in the lower half of the normal range in hypoparathyroid patients treated with calcium and vitamin D (19). Since PTH suppresses the secretion of sclerostin by bone, it is no surprise that hypoparathyroid patients have higher levels of sclerostin than euparathyroid healthy controls (23). Despite this higher sclerostin concentration, bone mass is increased in hypoparathyroidism, which may indicate that sclerostin's inhibitory action on bone formation is blunted in this disease.

Table 1. Signs and Symptoms of Chronic Hypoparathyroidism (excluding bone, kidney and quality of life, which are discussed in the text)

Organ System	Manifestations, Signs, Symptoms
Neuromuscular	Fatigue
	Generalized muscle weakness
	Muscle cramping (sometimes painful), manifested as carpal and or pedal spasms
	Neuromuscular irritability resulting in tetany
	Laryngospasm and stridor
	Bronchospasm and wheezing
	+Trousseau sign
	+Chvostek sign
	Electromyography: burst of rapid firing either spontaneously or induced by hyperventilation
	Elevated creatine kinase
Neurologic, psychiatric	Paresthesias and numbness especially around the mouth and in the fingers and toes
	Seizures, spells
	Poor memory and concentration
	Parkinsonism and chorea
	Pseudotumor cerebri
	Depression
	Anxiety
	Personality disturbances
	Basal ganglia and brain calcifications (Fahr's disease)
Cardiovascular	Congestive heart failure (cardiomegaly, pulmonary congestion, volume overload)
	Chest pain
	Arrhythmias
	Heart block
	ECG: prolonged QTc interval; changes suggestive of myocardial ischemia
Ophthalmologic	Papilledema
	Calcification of the cornea
	Cataract
Dermatologic	Alopecia
	Scaling of the skin
	Deformities of the nails
Gastrointestinal	Constipation
	Abdominal cramps
	Steatorrhea
Dental	Cemental hyperplasia
	Hypoplastic enamel
	Short rounded roots
	Hypodontia and delay or lack of tooth eruption
	Possibly widening of the periodontal ligament space

Histomorphometry and microcomputed tomography of bone biopsies

Hypoparathyroidism is associated with markedly reduced bone remodeling, as shown by histomorphometric assessment of the transiliac bone biopsy (12, 19, 24) (see Supplemental Table 2 and Figure 1). Iliac crest bone biopsies from 8 women and 4 men with vitamin D-treated hypoparathyroidism displayed a decreased resorption rate, and indices of bone formation and remodeling activation frequency were reduced by 54%-80%. The resorption depth was reduced, and the wall thickness of the cancellous osteons was 5 μm greater than the resorption depth. The remodeling cycle thus resulted in a slightly positive bone balance and, in each remodeling unit, slightly more bone was being deposited than removed (25). In a larger, comprehensive study in which remodeling variables were measured in 3 bone envelopes (cancellous, endocortical and intracortical), bone formation variables, including bone formation rate, osteoid surface and width, were consistently and substantially reduced by up to 5-fold across all envelopes. The reduction in bone formation rates was attributable, as demonstrated by reduced tetracycline uptake (Figure 1, panels E and F), to significant decreases in both mineralizing surface and mineral apposition rate. Despite a lack of difference between hypoparathyroid and control subjects in eroded surface, the

resorption rate was significantly reduced in the hypoparathyroid subjects, and again, this was consistently seen in all envelopes (12, 19). Microcomputed tomography of biopsies (26) allows structural analysis in 3-dimensions, and this technique confirmed the increase in cancellous bone volume in hypoparathyroidism and revealed not only an increase in trabecular thickness but also increases in trabecular number and connectivity (see Figure 1, panels A-D).

Fracture risk

Underbjerg et al (27), in a nationwide survey, identified 688 patients with postsurgical hypoparathyroidism due to nonmalignant causes, receiving conventional treatment with calcium and vitamin D metabolites for more than 6 months. Each case was matched for age and sex with 3 controls from the general population. The authors reported that long term overall fracture risk was not different from controls (HR 1.03; 95% CI 0.83–1.29), whereas the risk of fractures in the upper extremities was significantly decreased in patients with hypoparathyroidism [HR 0.69, (95% CI 0.49–0.97)]. In another study, Underbjerg et al (28) identified all 180 subjects diagnosed with nonsurgical hypoparathyroidism in Denmark between 1997 and 2012 (through registers and review of individual patient hospital charts). Patients were compared with an age- and gender-matched control group from the general population. While the overall fracture risk was similar between cases and controls, hypoparathyroid patients had, however, a greater risk of fractures in the upper extremities (HR 1.93; 95% CI, 1.31–2.85).

Two small studies have assessed vertebral fractures in patients with hypoparathyroidism. Fujiyama et al (29) evaluated 33 postmenopausal women who underwent total thyroidectomy due to thyroid cancer. Among them, 13 women became hypoparathyroid, whereas the remaining 20 retained normal parathyroid function. The incidence of spinal deformity, as assessed by spinal radiographs, was significantly lower in hypoparathyroid women than in controls. In contrast, a recent study demonstrated increased morphometric vertebral fractures in 16 patients with hypoparathyroidism, compared to 17 age-, and BMI-matched normal controls (30).

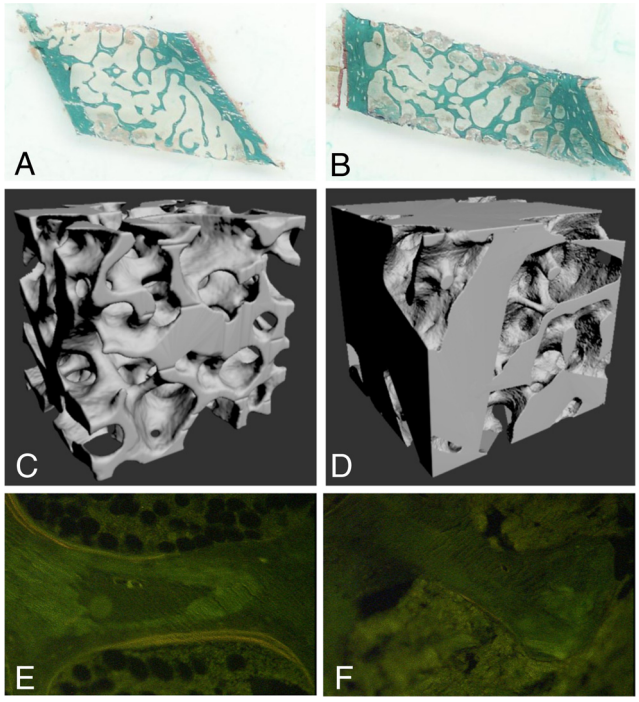

Figure 1. A, B: Low power images of entire Iliac crest bone biopsies from a control subject (A) and a hypoparathyroid subject (B). Goldner trichrome stain. Note the higher cortical thickness and cancellous bone volume in the hypoparathyroid subject. C,D: Microcomputed tomographic images of cancellous bone from a control subject (C) and a hypoparathyroid subject (D). Note the higher cancellous bone volume and dense trabecular structure in hypoparathyroidism. E,F: Tetracycline labels in a control subject (E) and a hypoparathyroid subject (F). Note reduction in tetracycline uptake in the hypoparathyroid subject reflecting reduced bone turnover. A,B,and E,F reproduced with permission from *J Bone Miner Res*. 2008;23:2018–24 (12).

Concluding statement. The low bone turnover in hypoparathyroidism is demonstrated by several techniques and results over time in higher bone mass. To what extent this is due to the lack of PTH and/or to the combined chronic therapy with calcium supplements and activated vitamin D metabolites is not well defined. The long-term effects of increased bone mass (likely to be beneficial) and low bone turnover (possibly deleterious to bone quality) on bone strength and fracture risk remain unclear.

Renal manifestations of chronic hypoparathyroidism in patients on treatment

Decreased PTH secretion or action results in decreased serum calcium and thus a decreased filtered calcium load and also decreased tubular reabsorption of calcium (TmCa). Thus, although hypoparathyroidism causes a relative hypercalciuria in relation to the prevailing hypocalcemia, the net effect is reduced urinary calcium excretion. Low levels of PTH also lead to increased renal TmP. The resulting hyperphosphatemia, in combination with low PTH levels, down-regulates renal production of $1,25(OH)_2$ D. The decreased serum $1,25(OH)_2$ D reduces active intestinal calcium absorption and to a lesser extent phosphorus absorption. Reduced filtered load of calcium and the reduced calcium absorption from the gut together result in a lower 24-hour urinary excretion of calcium, despite the decreased TmCa. This would theoretically decrease the risk of kidney stones in the untreated patient. The 24-hour urinary phosphorus remains normal, despite an increased TmP, because dietary phosphorus is usually

much in excess of requirements, and 24-hour urine largely reflects dietary phosphorus intake. PTH does not affect glomerular filtration significantly. However, the clinical use of calcium supplements, along with vitamin D and its active analogues, in an effort to normalize serum calcium and phosphate in hypoparathyroid patients often results in chronic hypercalciuria and increased urinary stone risk factors.

Overall, hypoparathyroidism and its long-term classical treatment (with oral calcium, calcitriol or other active vitamin D analogues) increases the risk of renal stone formation and nephrocalcinosis, and ultimately, decreased glomerular filtration rate (GFR), especially in those with episodes of treatment-induced hypercalcemia. These renal complications are the most serious long-term risks for patients with hypoparathyroidism (see below for Long-term Outcomes). Patients with activating CaSR mutations are even at higher risk (5, 31).

Concluding statement. Hypercalcemic episodes in the presence of hyperphosphatemia increase the risk of ectopic mineralization in the kidney and accelerate the risk of developing chronic kidney disease (CKD) in hypoparathyroidism. Patients should have regular assessments of renal function and should be considered for periodic renal imaging to evaluate for the presence of such ectopic calcifications. Ultrasound examination seems to be superior to CT for such diagnosis (32).

Quality of life

Many patients with hypoparathyroidism report symptoms that suggest impaired QOL (QoL) (5, 6). These include physical complaints such as fatigue, muscle spasms, pain, and paresthesia; cognitive symptoms such as "brain fog" and inability to concentrate; and emotional difficulties including depression and/or anxiety. Several publications have reported that patients with hypoparathyroidism have reduced QoL when compared to either normal population or suitable controls. A study from Germany of 25 women with postsurgical hypoparathyroidism showed a higher global complaint score compared to women who had thyroid surgery but had normal parathyroid function (33). The predominant increases were in subscores for anxiety. Similarly, in a recent study from the USA, 340 patients with postoperative hypoparathyroidism experienced symptoms that were considerably worse than anticipated by 200 healthy subjects (given the description of the disease) or by 102 experienced surgeons (34). In another study of postsurgical hypoparathyroidism, 688 patients from a Danish national registry had an increased risk of depression and other psychiatric symptoms when compared to 2752 matched controls (27). Idiopathic hypoparathyroidism was also associated with decreased QoL in a study from India showing these patients had higher proportion of neuropsychiatric and cognitive dysfunction than controls (34). Finally, an internet-conducted survey of 374 patients with hypoparathyroidism in the US showed that the majority had fatigue as well emotional and cognitive impairment (35).

Additional information on QoL in hypoparathyroid patients comes from baseline data obtained in treatment trials with PTH. These data are particularly useful as these patients are well characterized, and the tests of QoL are administered systematically and rigorously. In a trial of 69 participants from the US, all domains of QoL assessed by the SF36 were below normal at baseline with the T-scores ranging between –0.9 and –1.4 (36). The level of biochemical control of the participants was similar to general population of hypoparathyroid patients with 59.4% of subjects having serum calcium values within the reference range (8.6–10.2 mg/dL), and the mean (range) daily intakes of elemental calcium and calcitriol were 2.5 g (0–11) and 0.69 mcg (0–3), respectively. QoL was also examined in 62 adults with hypoparathyroidism from Denmark (37). Their SF36 scores were below mean for the normal population in 7 of 10 domains. On the WHO-5 Well-Being Index, 10% of these patients had scores consistent with a state of depression; 24% had scores indicating poor emotional well-being. When these same patients were asked about fatigue, 22% reported that they had been very tired, 37% reported that they had been tired most of the time for a prolonged period of time, and 22% did not report tiredness.

Concluding statement. While it is clear that hypoparathyroidism is associated with impaired QoL, the nature of this impairment and its relationship to biochemical control or other aspects of the disease are not well characterized. Further studies are needed to develop appropriate methods for assessing QoL, establish the relationship, if any, between biochemical variables and QoL, and examine the QoL response to current or emerging therapies.

Other manifestations

Other specific signs and symptoms, due to the many syndromic and nonsyndromic causes of hypoparathyroidism, are quite varied because of the broad spectrum of disorders that cause hypoparathyroidism (see Supplemental Table 3). These manifestations may include hearing loss, renal anomalies and dysfunction, dysmorphism, short stature, immunodeficiency, cardiac anomalies, skeletal abnormalities, and many others.

II. LONGTERM OUTCOMES AND COMPLICATIONS

Recent studies provide insight into the chronic complications and adverse outcomes that contemporary patients with chronic hypoparathyroidism may experience over time (27, 28, 31, 46). One chart review study done at two Boston tertiary care medical centers (31), included 120 patients (73% female) with permanent hypoparathyroidism due to acquired (89%: postsurgical, autoimmune and idiopathic) and congenital (11%: syndromic, nonsyndromic, and lifelong idiopathic) etiologies and followed for 7.4 +/- 5.1 year (from 1998–2009). Upon enrollment, disease had been present on average 17 +/- 16 years.

Records were reviewed for serum and urine biochemistries and renal and brain imaging when available. Defining an acceptable target serum calcium range as 7.5–9.5 mg/dL, Mitchell et al (31) found that the most recent serum calcium level was within that range in 71% of their patients. Furthermore, by their estimates, patients in this cohort spent 86% of the time they were followed in this target range. Just 53 patients had at least one 24 hour urinary calcium determination with 38% of that group having elevated urinary calcium levels (>300 mg/d). In terms of renal complications, two patients had undergone renal transplantation for nephrocalcinosis and CKD. Of the remaining patients, 31% of the group that had renal imaging (17/54 patients) demonstrated intra-renal calcification. Estimated glomerular filtration rates (eGFRs) were calculated and found to be < 60 ml/min/1.73 m^2 (stage 3 CKD or higher) in 41% of these patients with chronic hypoparathyroidism. This rate is estimated to be 2 to 17-fold higher than those for age-matched norms taken from the US-based NHANES (National Health and Nutrition Examination Survey; 1999–2006). Duration of disease and proportion of time with relative hypercalcemia (higher than the target range of 7.5–9.5 mg/dL) were the two features, by multivariate analysis, that were significantly associated with eGFR. Of the small number of patients with brain imaging (N = 31), 52% of them had basal ganglia calcification. Although the data were not prospectively gathered nor was the study controlled, these findings are still valuable for understanding particularly the effects of chronic hypoparathyroidism on the brain and kidneys.

In a case control study of 688 patients with hypoparathyroidism in Denmark (matched by age and gender to 2064 controls), Underbjerg et al (46) found an increased risk of renal complications (hazard ratio (HR) [HR], 3.67; 95% confidence interval (CI) [CI], 2.41–5.59) and of seizures (HR, 3.82; 95% CI, 2.15–6.79). There was no increased risk for arrhythmias or cardiovascular complications. In further studies on the same cohort, this group (27) examined the risk of psychiatric disease, infections, fractures, spinal stenosis, and cataracts. For the last three of these outcomes, there was no increased risk in patients with chronic postsurgical hypoparathyroidism. However, this patient group did show an increased risk of hospitalization for infection (HR, 1.42; 95% CI, 1.20–1.67) as well as depression/bipolar disease (HR, 1.99; 95%, CI 1.14–3.46).

A recent study assessed the morbidity and mortality of people with nonsurgical hypoparathyroidism in Denmark (28). Records revealed 180 persons with that diagnosis from 1977 to 2012, with 123 of them currently alive. Compared to controls [gender- and birth year (+/- 2 years)-matched], patients with hypoparathyroidism had no increased mortality. These hypoparathyroid subjects did show an increased HR for cardiovascular disease (HR 1.91; 95% CI 1.21–2.81); renal insufficiency (HR 6.01; 95% CI 2.45–14.75); hospitalization for psychiatric disease (HR 2.45; 95% CI 1.78–3.35); hospitalization for seizures (HR 10.05; 95% CI 5.38–18.72); hospitalization for infection (HR 1.94; 95% CI 1.55- 2.44); cataracts (HR 4.21; 95% CI 2.13–8.34); and fractures of the upper extremities (HR 1.93; 95% CI 1.31–2.85). The risks of renal stones and nephrocalcinosis were not increased. Risk of malignancy was significantly reduced (HR 0.44; 95% CI 0.24–0.82). Similar to those patients with postsurgical hypoparathyroidism there is a high burden of illness in patients with genetic or idiopathic etiologies for the disorder.

Concluding statement. Cross-sectional studies emphasize the importance of monitoring renal function, psychiatric complaints, and neurologic complications in the management of patients with chronic hypoparathyroidism. Clinical attention should be focused long-term on mitigating associated risk factors.

III. ETIOLOGIES OF HYPOPARATHYROIDISM

An essential issue to distinguish in the differential diagnosis of chronic hypocalcemia is whether the condition is due to PTH deficiency (described in detail below) or to defective actions of PTH caused by a rare group of disorders known as PHP (see Supplemental Table 3). In clinical practice, hypoparathyroidism results from a surgical procedure in approximately 75% of patients and is due to genetic, autoimmune, or idiopathic etiologies in the remainder (5–7). PHP is distinguished from hypoparathyroidism by the presence of high serum intact PTH levels. Otherwise, biochemically, the laboratory features of PHP patients overlap with those with hypoparathyroidism.

PHP is due to heterozygous loss of function mutations in the maternal *GNAS* gene encoding the alpha subunit of heterotrimeric G protein (G_s), as in PHP type 1a or 1c.

Such patients do not show an increase in urinary P excretion after exogenous administration of PTH. The same mutation in the parental gene does not cause PTH resistance as the paternal *GNAS* is always silenced in the proximal tubule of the kidney due to genetic imprinting. Such *GNAS* mutations are usually associated with a clinical phenotype as summarized in Supplemental Table 3 (39–43, 47). Individuals with PHP type 1a may also have resistance to other hormones that couple through G_s alpha, as this is a widely used signaling pathway for peptide hormones such as thyrotropin.

Patients with PHP type 1b have only selective renal resistance to PTH and do not have mutations in *GNAS* itself (see Supplemental Table 3). Rather, their functional defect is due to abnormal genetically defined imprinting of the GNAS gene in the kidney, usually due to deletions in the regulatory DNA sequences in *GNAS*. Differentiating the exact molecular etiology of PHP can be a diagnostic challenge, but biochemically, it is generally straightforward to distinguish PTH deficiency from PTH resistance (40, 43). The topic is covered more extensively in a companion article in this series. (ref).

Postsurgical hypoparathyroidism

The procedures responsible for postsurgical hypoparathyroidism include thyroid, parathyroid, laryngeal or other neck surgeries conducted for both benign and malignant conditions. Anywhere from 3 to 30% of patients with postoperative hypocalcemia will develop chronic hypoparathyroidism (48–54). Overall, postsurgical hypoparathyroidism is permanent in up to 7% of patients after total thyroidectomy (5–7).

Most endocrinologists define postsurgical hypoparathyroidism as the combined presence of hypocalcemia (serum calcium $<$ 2.0 mM or $\sim$8.0 mg/dL) with an inadequate PTH concentration [either frankly low or inappropriately normal (below 15 ng/L) intact PTH levels]. Permanent hypoparathyroidism is diagnosed when such a situation persists 6 or 12 months after a cervical surgical procedure. The causes are removal of the glands or permanent functional damage to glands left in situ (devascularization).

Uncomplicated thyroidectomies in most centers worldwide are increasingly performed with short-term in-hospital or outpatient perioperative observation (55, 56). Prediction and timely diagnosis and treatment of postsurgical hypoparathyroidism are, therefore, of utmost importance. Disease-related risk factors for postsurgical hypoparathyroidism include autoimmune thyroid disease [Graves´ disease or Hashimoto´s thyroiditis (48, 52, 57)], retrosternal goiter (58), and reoperation due to recurrence of goiter or for completion of surgery (52). Surgery-related risk factors include total vs subtotal thyroidectomy (48, 59), central node dissection in thyroid cancer (51, 60), low thyroid surgery volume or relative inexperience (61, 62), and inadequate visualization during thyroidectomy (63).

Preoperative vitamin D status is a risk factor for transient but not permanent hypoparathyroidism and, therefore, correction of vitamin D deficiency should be implemented preferably before surgery (64). Moreover, the number of parathyroid glands preserved in situ mainly determines the risk for transient and sustained hypoparathyroidism (48, 53). There is considerable controversy whether autotransplantation may help to preserve parathyroid function. While there is overall agreement regarding the need for autotransplantation when a parathyroid gland is completely devascularized, several surgeons in the past advocated parathyroid autotransplantation for glands not completely devascularized or even on a prophylactic basis (65, 66). Recent studies, however, provide evidence that autotransplantation of devascularized normal parathyroids does not completely prevent transient or permanent hypoparathyroidism (53). Even discolored, devascularized parathyroids may only be transiently impaired, and their function better preserved, if left in situ, than if autotransplanted (67). Therefore the autotransplantation of normal parathyroids can only be recommended when the gland is completely avascular.

Various protocols have been used for determining the predictive value of postoperative serum calcium and PTH concentrations at the time of skin closure after thyroidectomy up to the morning of the first postoperative day.

To summarize these studies, PTH levels during the first 24 hours after thyroidectomy seem to be more accurate for prediction of hypoparathyroidism than serum calcium concentrations. Accordingly oral calcium and active vitamin D is recommended when PTH levels are below 10–15 pg/ml postoperatively (54). Protocols with routine oral calcium and vitamin D substitution (68–70) have also been proposed in order to facilitate early discharge of patients after thyroidectomy.

Concluding statement. Postoperative hypoparathyroidism can best be avoided by routine identification of all parathyroid glands and meticulous preservation of their blood supply during surgery, which should be performed by surgeons with extensive experience with these procedures. Autotransplantation of parathyroid glands should be reserved for completely devascularized glands. Irrespective of the extent of surgery and the underlying thyroid disease, postoperative hypocalcemia (serum total calcium $<$ 2.0 mmol/l or $<$ 8.0 mg/dL) combined with low serum PTH ($<$15 pg/ml) indicate the highest risk for transient or even permanent hypoparathyroidism, and such

patients should be treated with prophylactic or therapeutic calcium and supplementation with activated vitamin D metabolites.

Genetic and autoimmune forms of hypoparathyroidism

Genetic forms of hypoparathyroidism occur as part of syndromes or as a nonsyndromic solitary endocrinopathy called isolated hypoparathyroidism (38, 71, 72). This section and the information in Supplemental Table 3 briefly review the genetics of these forms of hypoparathyroidism, the molecular basis when known, and clinical features of the disorders. A more detailed description of the pathophysiology and diagnostic testing of genetic forms of hypoparathyroidism is presented in an accompanying paper on Epidemiology and Diagnosis in this issue of the *Journal*.

The established syndromes causing hypoparathyroidism, in which the genetic defects are known, include the autoimmune polyendocrinopathy syndrome type 1 (APS1), DiGeorge syndrome (DGS) 1 and 2, hypoparathyroidism-deafness-renal dysplasia (HDR) syndrome, and Kenny-Caffey syndrome type 1 and 2 (see Supplemental Table 3). There remain a number of syndromes in which the clinical features are recognized (Barakat and Dubowitz syndromes, for example), but the genetic bases have not yet been established. These syndromic forms of hypoparathyroidism may be inherited as autosomal dominant or autosomal recessive disorders. The very rare and complex syndromes due to mitochondrial DNA mutations and deletions can also include hypoparathyroidism as one feature (see Supplemental Table 3) (38, 72–74).

Several molecular defects causing isolated hypoparathyroidism have also been identified [eg, mutations in the PTH gene, transcription factor *GCM2*, *CASR*, *G alpha 11* (*Gα11*), and *SOX3*]. These nonsyndromic forms of hypoparathyroidism may be inherited as autosomal dominant, autosomal recessive and X-linked recessive disorders (38, 72, 75–79). Gain-of-function *CASR* mutations result in autosomal dominant hypocalcemia type 1 (ADH1). ADH1 patients generally have normal serum PTH concentrations and hypomagnesemia, and treatment with vitamin D or its active metabolites or analogues to correct the hypocalcemia may result in marked hypercalciuria, nephrocalcinosis, nephrolithiasis and renal impairment (75). Gain-of-function *Gα11* mutations result in ADH2, another form of isolated hypoparathyroidism (76–78). ADH2 patients have clinical features that are similar to ADH1 (75, 76). A clinical approach to genetic testing in a patient who has hypoparathyroidism and in whom other causes have been excluded is discussed in the paper on Diagnosis.

Concluding statement. When there is a high suspicion of a genetic etiology (eg, young age of onset or family history of autoimmunity or consanguinity), the patient should be offered genetic counseling and germline mutation testing.

Magnesium disorders

Magnesium regulates PTH secretion (80). Magnesium binds to and activates the CaSR and decreases PTH synthesis and secretion. Magnesium is also involved in the activation of adenylyl cyclase and in intracellular signaling by cyclic AMP. Activating mutations of the *CASR* result in hypocalcemia, hypomagnesemia, and low PTH levels. In chronic kidney disease (stages 4–5), urinary magnesium excretion decreases resulting in hypermagnesemia. Hypermagnesemia also occurs with lithium therapy or after excessive ingestion or intravenous (IV) administration of magnesium (eg, as tocolytic therapy). Inactivating mutations of the *CASR* (FHH type 1) result in hypercalcemia, hypermagnesemia, and high normal PTH levels. Hypermagnesemia may cause hypocalcemia due to the inhibition of PTH release. Very low serum concentrations of magnesium, however, can also markedly decrease PTH secretion and mimic PTH deficiency. Hypomagnesemia may be due to decreased intake, decreased absorption, increased losses, and redistribution (44).

Mutations in the epithelial cation channel *TRMP6* result in familial hypomagnesemia with secondary hypocalcemia (FHSH) with decreased intestinal magnesium absorption and increased renal magnesium losses (81). Mutations in claudin-16 and claudin-19 result in familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) (82). Long-term proton pump inhibitor therapy may result in hypomagnesemia due to enhanced GI magnesium losses, possibly due to inhibition of TRPM6-mediated active transport of magnesium, as a consequence of altered intestinal pH (83, 84). Diuretics, certain antibiotics, calcineurin inhibitors, and epidermal growth factor receptor antagonists may down-regulate TRPM6, thereby, increasing urinary magnesium losses (85). Activating mutations of the *CASR* result in hypocalcemia, hypomagnesemia, and low normal PTH (86). Severe hypomagnesemia can be corrected by higher intake of magnesium which corrects the functional hypoparathyroidism. More detailed information about disorders of magnesium homeostasis is presented in Supplemental Table 3.

Other causes of hypoparathyroidism

Once postsurgical and genetic etiologies of hypoparathyroidism (both syndromic and nonsyndromic) and magnesium depletion and excess are excluded, there remain only a few conditions that cause the disorder (87). Infil-

trative diseases like Wilson's disease (copper deposition) (88–90) and hemochromatosis (iron deposition) can produce hypoparathyroidism. Iron overload can be due either to primary hemochromatosis or secondary to chronic transfusions as in patients with thalassemia. Tissue deposition of iron in these settings can produce hypoparathyroidism. When hypoparathyroidism occurs, it is often accompanied by other endocrinopathies such as diabetes, hypothyroidism, osteoporosis, and hypogonadism (91–98). The prevalence of hypoparathyroidism in cohorts of patients with thalassemia undergoing chronic transfusions and iron chelation therapy varies from ~10%-24%. The rate of this complication, like others in states of iron overload, decreases with aggressive chelation and is increased when serum ferritin levels are > 2500 mcg/L (95). Rarely hypoparathyroidism is due to destruction of the glands by infiltrating secondary tumors (99, 100) or by ionizing radiation (101, 102).

Conclusions

In conclusion, hypoparathyroidism is a rare endocrine disease, most frequently due to surgical damage to the parathyroid glands. Patients undergoing thyroid surgery are at risk for postsurgical hypoparathyroidism and should routinely have serum calcium and intact PTH levels assessed either 4 to 6 hours or within 24 hours of surgery. If the serum total calcium concentration is < 2.0 mM and if PTH is < 10–15 pg/ml, then the patient, independent of the extent of resection and type of disease, has a greater risk of permanent hypoparathyroidism.

Hypoparathyroidism can also be due to destruction by an autoimmune mechanism or the toxicity from tissue overloading by such agents as iron or copper. Severe magnesium deficiency may be responsible for reversible functional hypoparathyroidism and respond to magnesium repletion. A large number of genetic diseases can cause either isolated or syndromic forms of hypoparathyroidism. An affected patient will likely require the input of specialists to guide genetic testing, treatment, and family planning.

The long-term consequences of hypoparathyroidism can be substantial. Several studies report impaired QoL in patients treated for hypoparathyroidism with calcium and vitamin D, and preliminary data suggest that PTH therapy may improve QoL. The most severe long-term consequences of hypoparathyroidism treated with oral calcium and active vitamin D supplements are due to ectopic calcification of soft tissues. The risk of kidney stones, nephrocalcinosis and even renal failure is markedly increased. Patients should be monitored for renal dysfunction by renal ultrasonography and regular biochemical assessment of renal function. These patients are also at an increased lifetime risk of hypocalcemic seizures and calcification of the basal ganglia. Hypoparathyroid patients chronically treated with calcium and vitamin D have higher BMD and lower bone turnover, but it is presently unclear if this impacts fracture risk.

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Address all correspondence and requests for reprints to: Dolores Shoback, Endocrine Research Unit, San Francisco Department of Veterans Affairs Medical Center, 1700 Owens Street, third floor Room 369, University of California, San Francisco, San Francisco, CA 95 158, Telephone: 415.221.4810 and 415.525.0552, Fax: e-mail: dolores.shoback@ucsf.edu.

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