CLINICAL PRACTICE

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Primary Hyperparathyroidism

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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.*

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A 57-year-old woman has a fasting serum calcium level of 10.8 mg per deciliter (2.70 mmol per liter; reference range, 9.0 to 10.2 mg per deciliter [2.24 to 2.56 mmol per liter]) detected on routine laboratory testing. On repeat testing a week later, the level is 10.5 mg per deciliter (2.62 mmol per liter). The serum phosphorus level is 2.4 mg per deciliter (0.75 mmol per liter), the estimated glomerular filtration rate (eGFR) more than 60 ml per minute, the total serum protein level 7.0 g per liter, and the albumin level 4.0 g per liter. The parathyroid hormone (PTH) level is 95 pg per milliliter (reference range, 20 to 65). The patient's last menstrual period occurred at 54 years of age. She has no history of fracture or renal stones and no family history of hypercalcemia. Her mother fractured her hip slipping on ice at 70 years of age. How should this patient's condition be evaluated and treated?

THE CLINICAL PROBLEM

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

In highly resourced health care systems, in which serum calcium is routinely measured, patients with primary hyperparathyroidism typically present with mild-to-moderate hypercalcemia and nonsuppressed or high PTH levels, measured in an immunoassay that predominantly detects intact hormone. The prevalence of the condition in the United States has been estimated at 23 cases per 10,000 women and 8.5 per 10,000 men, with an incidence of 66 cases per 100,000 person-years in women and 25 per 100,000 person-years in men.[1] Patients with normocalcemic hyperparathyroidism have consistently normal serum calcium levels and have hypercalciuria less often than patients with hypercalcemic hyperparathyroidism, but they are not spared the skeletal complications of the disease.[2] In one cohort of U.S. patients with mild-to-moderate hypercalcemia, approximately 50% underwent surgical treatment. During 15 years of follow-up, 30 to 40% of the remaining patients ultimately had surgery.[3] In resource-limited health care settings, patients present with more advanced disease,[4,5] and those with few or no symptoms are presumably less likely to be evaluated or treated.

Approximately 80% of patients with primary hyperparathyroidism have a single parathyroid adenoma, 10 to 11% have more than one adenoma, and less than 10% have hyperplasia of all four glands.[6] Parathyroid carcinoma causes less than 1% of cases of hyperparathyroidism.

SYMPTOMS

In resource-rich health care systems, less than 20% of patients present with overt symptoms. Occasionally, patients present with pain from a fracture or from renal

KEY CLINICAL POINTS

PRIMARY HYPERPARATHYROIDISM

- In primary hyperparathyroidism, serum calcium levels are elevated in the context of nonsuppressed parathyroid hormone levels. It is most often caused by a single parathyroid adenoma.
- Patients with mild hyperparathyroidism are at increased risk for renal stones, cortical bone loss, and fractures.
- Evaluation should include measures of serum calcium, intact parathyroid hormone, 25-hydroxyvitamin D, glomerular filtration rate, 24-hour urine calcium excretion, and bone density (including the distal third of the radius), as well as a renal ultrasound examination to detect stones.
- Surgery is recommended for patients younger than 50 years of age and for patients with clinically significant hypercalcemia, osteoporosis or a fragility fracture, renal calculi, hypercalciuria (especially with a lithogenic urine biochemical profile), or impaired renal function.
- Medical management includes correction of dietary calcium and vitamin D insufficiency. Cinacalcet lowers serum calcium levels but does not affect rates of bone loss. Bisphosphonates improve bone density, but whether they reduce the risk of fracture is unknown.
- Surgery does not correct cardiovascular abnormalities in hyperparathyroidism, and whether it alleviates psychiatric and cognitive deficits is a subject of controversy.

colic. Obtundation, neuromuscular weakness, or both from severe hypercalcemia are very uncommon and are usually caused by a large adenoma or, in rare cases, parathyroid carcinoma. Moderate-to-severe hypercalcemia can cause constipation and is a risk factor for pancreatitis (Fig. 1). Dehydration or immobilization can worsen hypercalcemia. Hyperparathyroidism is not causally associated with peptic ulcer disease but, in multiple endocrine neoplasia type 1 syndrome, patients can have parathyroid tumors and gastrinomas. Fatigue, depression, and impaired memory are not infrequent, but a causal link between these conditions and parathyroid disease is uncertain. In resource-limited health care settings, patients present with higher serum calcium levels and are more often symptomatic.[4,5]

COMPLICATIONS

BIOCHEMICAL PROGRESSION

In most asymptomatic patients, the serum and urine biochemical profiles remain stable for years. In one study involving 49 asymptomatic patients who did not meet criteria for surgery and who were followed without intervention for 15 years, only slight changes in serum and urine calcium and PTH levels occurred, although the number of patients who were followed beyond 5 years was small.[3] In another study involving 73 patients with asymptomatic hyperparathyroidism who underwent observation for at least 5 years,[7] 5 patients (7%) underwent parathyroid surgery for hypercalcemia between years 3 and 5 (Bollerslev J: personal communication).

BONE LOSS AND THE RISK OF FRACTURE

Skeletal health is a frequent concern in hyperparathyroidism. In one study, 23% and 58% of patients with hyperparathyroidism had bone-density values in the femur and radius, respectively, that were less than 80% of that among age- and sex-matched persons who did not have the condition.[8] In another study, it was estimated that 15% of patients with hyperparathyroidism had osteopenia in the lumbar spine.[9] A more recent report included 4016 unselected patients undergoing bone densitometric measurements, of whom 451 had z scores for bone mineral density that were below –2.0 SD at either the spine or the femoral neck; of these patients, 52 (12%) had primary hyperparathyroidism, which suggested that the prevalence of hyperparathyroidism is higher among patients with low bone mineral density.[10]

Bone mass usually declines, albeit slowly, in patients with hyperparathyroidism. During a 15-year observational study, spinal bone mineral density was preserved, whereas bone density in the femoral neck and radius slowly declined.[3] Nonetheless, studies have shown an increased risk of fractures of the spine, wrist, rib, and pelvis.[11-13] Whether there is an increased risk of hip fracture is less clear: two studies showed a nonsignificantly higher risk of femur fracture (of the proximal femur in one study and the femoral neck in the other) in patients with hyperparathyroidism than in persons without the condition.[11,12] High rates of bone remodeling and impaired bone microarchitecture and quality may contribute to the risk of fracture.[14]

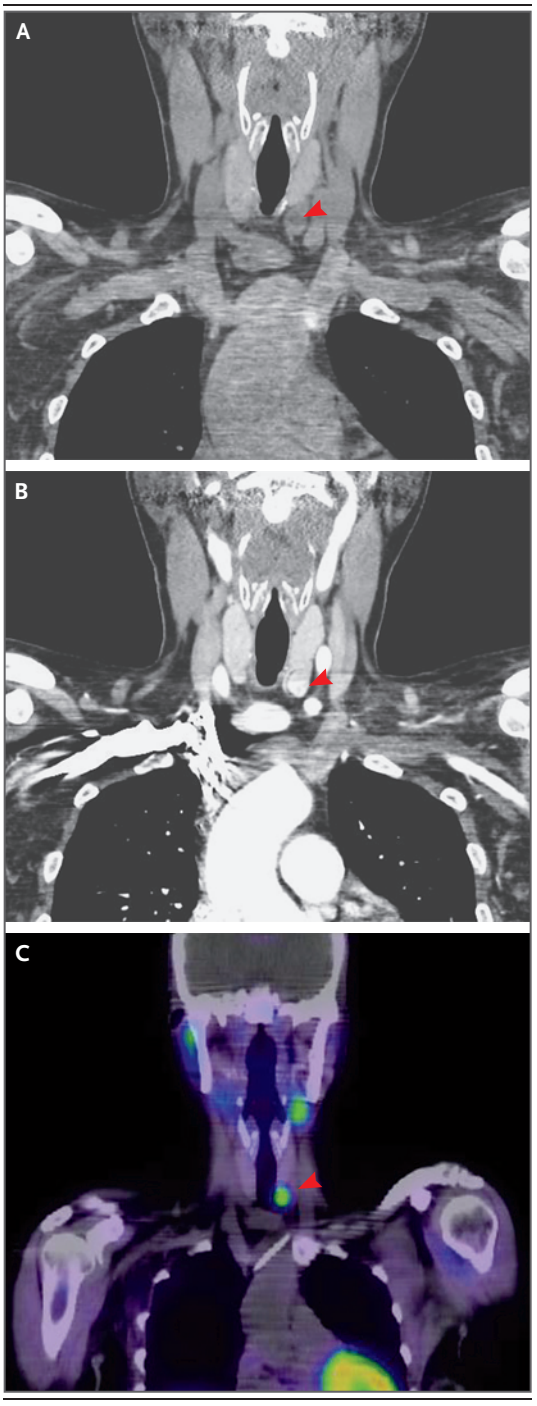

Figure 1. Computed Tomographic (CT) Scan Showing a Parathyroid Adenoma.

Shown is a dynamic (4D) CT scan of a left-inferior-pole parathyroid adenoma in a 43-year-old woman with a serum calcium level of more than 13 mg per deciliter (3.24 mmol per liter) and severe pancreatitis. The parathyroid hormone level was 408 pg per milliliter. At surgery, a single 900-mg parathyroid adenoma was removed. Noncontrast coronal CT imaging (Panel A) reveals a hypodense nodule relative to the thyroid gland, inferior to the left thyroid lobe (red arrowhead). The postcontrast coronal CT image (Panel B) shows diffuse enhancement of the left inferior nodule (red arrowhead). A fused CT and sestamibi image (Panel C) shows increased sestamibi uptake in the left lower parathyroid adenoma (red arrowhead).

NEPHROLITHIASIS

In mild hyperparathyroidism, renal function is not compromised. Symptomatic renal stone disease is less frequent than in the past, at least in resource-rich health care systems. A U.S. referral urology service reported that 3% of 1190 adults who underwent evaluation for renal stones had hyperparathyroidism.[15] The estimated prevalence of radiographically identified renal stones among patients with primary hyperparathyroidism in industrialized nations has ranged from 7 to 20%.[16-18]

As compared with the general population with renal stones, patients with hyperparathyroidism and renal stones have higher 24-hour urinary calcium levels[15] and higher serum 1,25-dihydroxyvitamin D levels, whereas serum calcium, PTH, and 25-hydroxyvitamin D levels are not significantly different.[19,20] Hypocitraturia and hyperoxaluria are also reported risk factors for renal stone disease in these patients.[21] Patients with mixed calcium oxalate–apatite stones (apatite content >5% and <30%) or pure apatite stones may be more likely to have hyperparathyroidism than patients with renal stones that are more than 90% calcium oxalate.[22]

NEUROPSYCHIATRIC DISEASE

Depression, anxiety, and difficulty with memory and concentration are frequently observed in patients with primary hyperparathyroidism. However, the pathogenesis of these disorders in hyperparathyroidism is uncertain.

CARDIOVASCULAR DISEASE

The incidence of hypertension, changes in left ventricular mass and function, and other adverse cardiac changes have been observed to be higher among patients with primary hyperparathyroidism than in the general population.[23] Observational studies have reported increased risks of death from any cause and death from cardiovascular causes in patients with hyperparathyroidism.[24,25]

STRATEGIES AND EVIDENCE

DIAGNOSIS AND EVALUATION

In addition to calcium levels that are usually high and associated PTH levels that are not appropriately suppressed (and therefore inappropriately normal or high), serum levels of 25-hydroxyvitamin D are usually normal or low-normal in patients with hyperparathyroidism. These normal or low-normal levels of serum 25-hydroxyvitamin D are found in part because PTH increases conversion of this metabolite to 1,25-dihydroxyvitamin D; levels of 1,25-dihydroxyvitamin D are correspondingly often high or high-normal.

Primary hyperparathyroidism should be distinguished from other causes of elevated levels of intact PTH. Secondary hyperparathyroidism, a physiologic response to hypocalcemia, is seen in association with severe vitamin D deficiency, intestinal calcium malabsorption, and chronic kidney disease (Table 1). Tertiary hyperparathyroidism occurs in some patients with end-stage renal disease when chronic hypocalcemia, hyperphosphatemia, and impaired synthesis of 1,25-dihydroxyvitamin D lead to parathyroid hyperplasia and eventually to hypercalcemia.

Several uncommon genetic disorders also cause hyperparathyroidism. Patients with familial hypocalciuric hypercalcemia type 1 have heterozygous loss-of-function mutations in the calcium-sensing receptor and lifelong modest elevations in serum calcium with low calcium excretion in the urine.[26] These patients generally do not require treatment. Hyperparathyroidism due to four-gland hyperplasia is seen in multiple endocrine neoplasia type 1 and type 2 syndromes.[27] Patients with the hyperparathyroidism–jaw tumor syndrome often have more severe hypercalcemia than do patients with sporadic disease due to a benign adenoma but can present with what appears to be typical primary hyperparathyroidism.[27] They are at increased risk for recurrent disease and parathyroid carcinoma. In these genetic syndromes, a detailed family history is the most important diagnostic tool, followed by genetic testing if appropriate.

Long-term lithium therapy can cause a clinical picture indistinguishable from hyperparathyroidism. Although thiazide diuretics are often cited as worsening hypercalcemia in patients with hyperparathyroidism, this may not be the case in those with mild disease (serum calcium level, <11.5 mg per deciliter [<2.88 mmol per liter]; serum PTH level, <2.5 times the upper limit of the normal range).[28] Primary hyperparathyroidism is uncommon among children and adolescents; when it occurs, the levels of calcium in serum are often higher and germline mutations more frequent than among adults.

After the diagnosis of hyperparathyroidism has been made, if there is clinical concern about nephrolithiasis, a renal ultrasound examination should be ordered. A 24-hour urine calcium measurement can aid in assessing the risk of stone formation. The effects of hyperparathyroidism on bone density are assessed by bone densitometry at the spine and hip, as well as in the distal third of the radius, which is a cortically enriched site and is particularly sensitive to the effects of hyperparathyroidism.[8,9]

SURGICAL MANAGEMENT

Surgery remains the only definitive treatment for hyperparathyroidism. Guidelines from the 4th International Workshop[29,30] recommend surgery for patients whose serum calcium level is more than 1.0 mg per deciliter (0.24 mmol per liter) above the upper limit of the normal range, for patients younger than 50 years of age, and for men and perimenopausal or postmenopausal women 50 years of age or older who have T scores of –2.5 or lower at a central bone densitometry site or in the distal third of the radius or who recently have had a fragility fracture. A glomerular filtration rate of less than 60 ml per minute, renal stones, and a urine calcium level of more than 400 mg per day (10.0 mmol per day) (particularly if the hypercalciuria is accompanied by urine biochemical measures that are indicative of an increased risk of stone formation) are each considered indications for surgery. In patients with normocalcemic hyperparathyroidism, these same criteria apply, with the exception of the serum calcium criterion. The American Association of Endocrine Surgeons also recommends surgery for hyperparathyroidism accompanied by neurocognitive or neuropsychiatric findings like those quantified using the Short Form 36 General Health Survey, although they note that the strength of evidence is weak (see below).[31]

Although parathyroid imaging is not necessary to establish a diagnosis of primary hyperparathyroidism, four preoperative imaging methods are routinely used to localize abnormal parathyroid

Table 1. Typical Findings in Hyperparathyroidism.

Finding	Primary Hyperparathyroidism	Normocalcemic Hyperparathyroidism	Secondary Hyperparathyroidism	Tertiary Hyperparathyroidism	Familial Hypocalciuric Hypercalcemia
Family history of hypercalcemia	No	No	No	No	Yes; sometimes with a history of unsuccessful parathyroid surgery
Lifelong hypercalcemia	No	No	No	No	Yes
Parathyroid hormone level	High	High	High	High	Normal to high-normal (approximately 75%) or high (approximately 25%)
Calcium	High	Normal	Low or low-normal	High	Normal or high
Phosphorus	Normal or low-normal	Normal or low-normal	Variable; can be high with renal insufficiency	Usually high owing to renal failure	Normal
25-hydroxyvitamin D	Normal	Normal	Normal or more often low, depending on cause (e.g., <20 ng/ml in vitamin D deficiency)	Normal	Normal
1,25-dihydroxyvitamin D	Often high or high-normal	Variable but not low	Variable; often low in renal insufficiency, high in calcium malabsorption	Low	Normal
Bone mineral density	Can be low, particularly at cortical sites	Can be low, particularly at cortical sites	Can be low with long-standing disease	Often low, particularly at cortical sites	Normal
24-hr urine calcium	Normal or high	Normal or high	Very often low	Low	Low, with calcium:creatinine clearance ratio <0.010*

* The calcium:creatinine clearance ratio is calculated as (urine calcium×serum creatinine)/(urine creatinine×serum calcium), with all measurements in the same units (i.e., millimoles per liter or milligrams per deciliter).

Table 2. Imaging Methods Used to Localize Abnormal Parathyroid Tissue.

Imaging Method	Sensitivity*	Positive Predictive Value*	Characteristics, Advantages, and Limitations
	percent		
Ultrasonography	70.4–81.4	90.7–95.3	Safe, involves no radiation; adenomas are hypoechoic, posterior to the thyroid gland, with peripheral vascularity; cannot detect mediastinal adenomas
Technetium-99m sestamibi scanning with single-photon-emission CT	64–90.6	83.5–96.0	Helps with localization; can be used to detect ectopic parathyroid tissue
Dynamic (4D) CT imaging	89.4	93.5	Useful for identifying multiple or ectopic adenomas and in patients requiring a second operation; exposes the thyroid gland to ionizing radiation
Magnetic resonance imaging	88	90	Same principles as 4D CT imaging, but obviates concerns about radiation

* Data are from Cheung et al.[32] and Nael et al.[33] CT denotes computed tomography.

tissue[32,33] (Table 2 and Fig. 1, and Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Precise preoperative localization enables minimally invasive parathyroidectomy, in which a single offending adenoma can be resected with limited operative time (15 to 20 minutes) — sometimes using just a cervical block with sedation.

Surgical treatment of hyperparathyroidism should incorporate intraoperative PTH measurements where available. After removal of a single adenoma, the intraoperative PTH should decrease by at least 50% and into the normal range.[34] Intraoperative measurements of PTH are particularly valuable when more than one gland is abnormal (Fig. 2). In centers with expertise in parathyroid surgery, cure rates are above 95%.[6,35] Recurrent hyperparathyroidism after surgery occurs infrequently, but, in experienced hands, a second procedure is often curative. In multigland hyperplasia, the goal is to reduce the mass of abnormal tissue to normalize the serum calcium level without causing permanent hypoparathyroidism. Complications are rare when the procedure is performed by an experienced surgeon. Potential complications (all uncommon) include recurrent laryngeal nerve injury (<1% of cases), wound infection, and bleeding. Postoperative transient hypocalcemia (usually mild) occurs in 15 to 30% of cases but can be minimized by the appropriate use of calcitriol and supplemental calcium.[36]

Surgical cure is followed by an increase in bone mass in increments in the range of 2 to 4% in the first postoperative year.[37-40] Consequently, it is prudent, except in severe cases, to withhold antiosteoporotic therapy after surgery until it is clear to what extent bone mass has improved. Preoperative serum levels of c-telopeptide of type 1 collagen are correlated with the degree of gain in bone mass after surgery.[41] In a 15-year retrospective study, patients who received a surgical cure had a 10-year absolute risk of hip fracture that was 64% lower than that among patients who had not received any treatment.[42] An earlier controlled cohort study also reported a 50% lower risk of hip and upper arm fracture in association with surgery.[43] Successful surgical cure is associated with a lower risk of recurrent stone passage,[44,45] and the urine calcium level usually declines.

Randomized, controlled trials have not consistently shown alleviation of hyperparathyroidism-related neurocognitive and emotional symptoms after surgical cure.[46] Similarly, whether surgery reduces the cardiovascular disease risk associated with hyperparathyroidism remains unclear. Observational data and follow-up data from randomized trials comparing parathyroidectomy with observation have shown no significant improvement in blood pressure or markers of metabolic syndrome[47] and have shown, at most, modest changes in echocardiographic measures.[48,49]

MEDICAL MANAGEMENT

For patients who decline or are not candidates for surgery, medical therapies have been used to address hypercalcemia, bone disease, and hyper-

Baseline Intraoperative Parathyroid Hormone Level
84 pg/ml

After Resection of the Left Inferior Parathyroid Gland	
Time (min)	Parathyroid Hormone (pg/ml)
0	96
5	81
10	75
15	67
20	61

After Resection of the Right Inferior Parathyroid Gland	
Time (min)	Parathyroid Hormone (pg/ml)
0	32
5	24
10	21
15	19
20	17

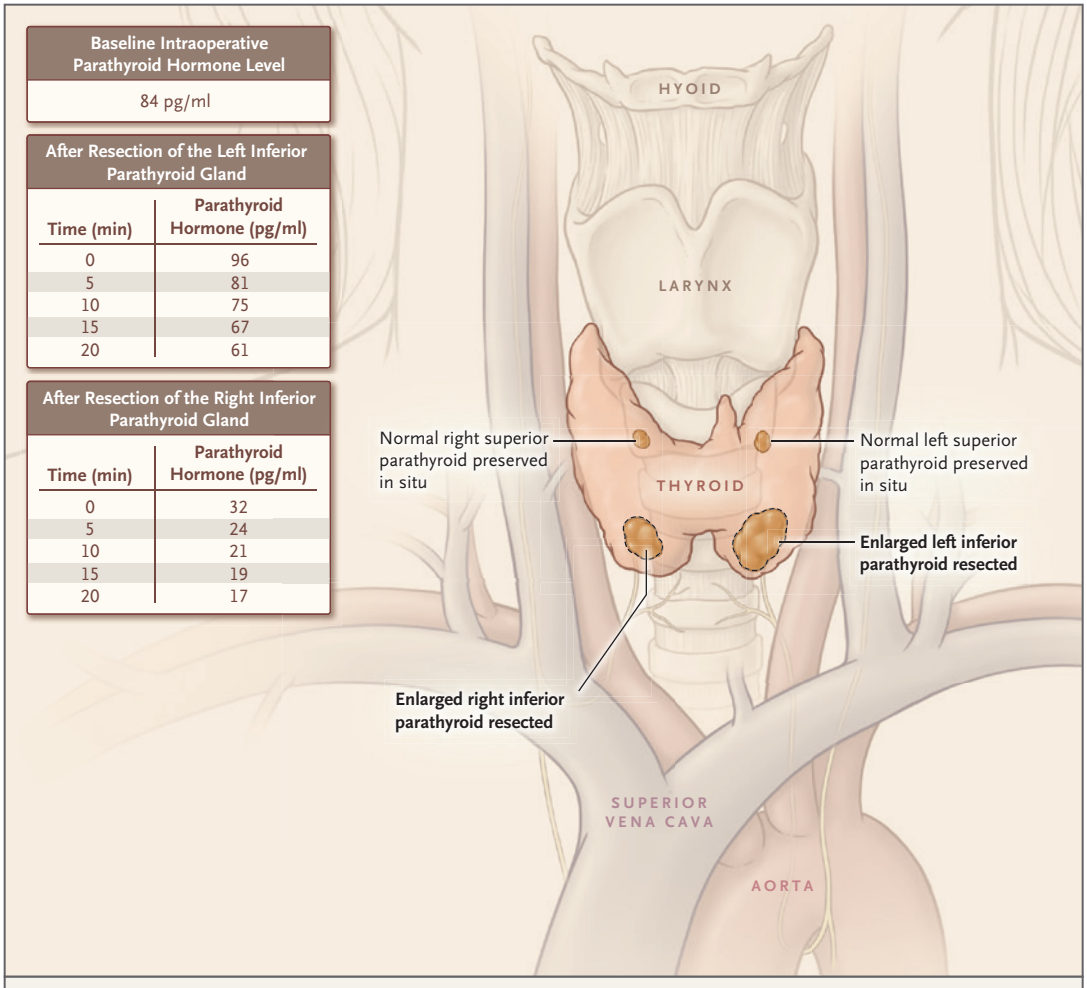

Figure 2. Parathyroid Hormone Measurements before and after Parathyroid Resection.

Shown are the intraoperative parathyroid hormone measurements in a 59-year-old woman with osteoporosis who was found to have a serum calcium level of 10.4 mg per deciliter (2.60 mmol per liter), a serum phosphorus level of 2.4 mg per deciliter (0.75 mmol per liter), a parathyroid hormone level of 122 pg per milliliter, a serum creatinine level of 0.8 mg per deciliter (70 μmol per liter), a 25-hydroxyvitamin D level of 37 ng per milliliter, and a urine calcium level of 241 mg per day (6.0 mmol per day). After resection of the left inferior parathyroid adenoma, the intraoperative parathyroid hormone level did not drop appropriately. Resection of the right inferior parathyroid adenoma resulted in normalization of the intraoperative parathyroid hormone level. Nine days after surgery, the serum calcium level was 8.9 mg per deciliter (2.22 mmol per liter) and the parathyroid hormone level was 15 pg per milliliter.

calciuria in hyperparathyroidism. The guidelines for medical monitoring[30] recommend annual measurement of serum calcium levels and repeat measurements of bone density (spine, hip, and radius) annually or biennially, with radiographs of the spine or vertebral fracture assessment if height loss occurs or there are symptoms of a vertebral facture. Imaging of the kidneys and a 24-hour urine biochemical profile to assess the risk of renal stone formation are recommended annually for patents with a history of renal stones or prevalent renal calculi.

Vitamin D and Calcium

Deficiencies in vitamin D and dietary calcium worsen hyperparathyroidism, so patients should have a calcium-sufficient diet (1000 to 1200 mg per day) and maintain a serum 25-hydroxyvitamin D level in the range of 20 to 30 ng per milliliter, with the use of vitamin D supplements as

necessary.[50] Although calcium supplements do not worsen hypercalcemia in most patients with mild disease,[51] dietary sources of calcium are always preferred, and patients should be carefully monitored if supplements are prescribed. Hydration is important, to prevent worsening hypercalcemia and reduce the risk of nephrolithiasis.

Calcimimetic Therapy

Cinacalcet is an allosteric activator of the calcium-sensing receptor and in hyperparathyroidism sensitizes that receptor to serum calcium which, when activated, suppresses the secretion of PTH.[52] In a double-blind, randomized trial, after 1 year of treatment, the serum calcium level was 1 mg per deciliter lower and the mean PTH level 19% lower among patients with hyperparathyroidism who received cinacalcet than among those who received placebo, but cinacalcet had no significant effect on bone loss. In the 4.5-year open-label extension study in which all the patients received cinacalcet, serum calcium levels remained normal and PTH levels remained below baseline at the end of the study, but there continued to be no substantial change in rates of bone loss.[53]

Antiresorptive Therapy

A meta-analysis of 25 observational studies and 8 randomized, controlled trials evaluating surgery as compared with bisphosphonate therapy showed similar increases in bone mass in the spine and femoral neck at 1 year in the two treatment groups. Fewer data were available for analysis at 2 years, but the increase in bone mass was still similar in the two groups.[39] Data from long-term studies or studies with fracture as an outcome that can inform the use of anti-resorptive therapy in primary hyperparathyroidism are limited. Oral bisphosphonates do not correct the hypercalcemia in hyperparathyroidism.

Thiazide Diuretics

In a retrospective analysis involving 72 patients, hydrochlorothiazide (12.5 mg to 50 mg daily) was found to significantly reduce urinary calcium and parathyroid hormone levels with no increase in serum calcium.[28] Because reducing urinary calcium excretion reduces the risk of calcium stone disease,[54] thiazides may be considered for hypercalciuric patients who are deemed at risk for nephrolithiasis. Careful monitoring of blood calcium is still advisable.

AREAS OF UNCERTAINTY

The relationship between neurocognitive and emotional problems and hyperparathyroidism remains unclear. There is heterogeneity in the end-organ effects of similar levels of hyperparathyroidism and in the response to changes in calcium intake.[55] Research is needed to better predict which patients who do not meet the criteria for surgery are at greatest risk for fracture and other complications. Although rates of surgical cure are high, late recurrences still occur in what appears to be sporadic primary hyperparathyroidism, so a more comprehensive understanding of disease pathogenesis is still needed.

CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette appears to have mild hyperparathyroidism, given her mild hypercalcemia, normal eGFR, and absence of complications, but further evaluation is warranted. The maternal history of fragility fracture increases her risk of fracture. She is early in menopause and may have accelerated bone loss because of both estrogen deficiency and parathyroid disease. If a bone densitometric study shows a T score of –2.5 or less at any site, I would recommend surgery. Sonographic evidence of renal stones or a urine calcium level of more than 400 mg per day, particularly if accompanied by hyperoxaluria or hypocitraturia, would prompt a surgical referral.

If the patient does not have indications for surgery now or prefers medical management, I would advise a calcium-sufficient diet (1000 mg per day) and use a vitamin D supplement if necessary to maintain her serum 25-hydroxyvitamin D level in the range of 20 to 30 ng per milliliter. I would stress the importance of hydration and encourage regular exercise. If her urine calcium level was higher than 400 mg per day, I would consider using a thiazide. If her bone density was in the osteoporotic range, I would discuss antiresorptive therapy. I would see her annually to reassess her symptoms and biochemical profile and would repeat the renal ultrasound ex-

amination if symptoms developed that suggested the presence of a renal stone. Depending on her baseline bone mineral density and whether antiresorptive therapy was initiated, I would repeat the bone densitometric study in 2 years.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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