

CLINICAL PRACTICE

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 authors' clinical recommendations.

A 62-year-old woman is found on routine laboratory testing to have a serum calcium level of 10.8 mg per deciliter (2.7 mmol per liter) (normal range, 8.4 to 10.4 [2.1 to 2.7]). The serum intact parathyroid hormone (PTH) concentration is 70 pg per milliliter (normal range, 15 to 75). Her history is notable only for hypertension that is well controlled with an angiotensin-receptor blocker; there is no history of kidney stones or fractures. Her family history is negative for hypercalcemia or endocrine tumors. Her 24-hour urinary calcium and creatinine levels are 280 mg and 1050 mg, respectively, and the ratio of calcium to creatinine clearance is 0.025. Bone densitometry shows T scores at the lumbar spine of -1.8 , at the total hip of -2.2 , and at the distal third of the radius of -3.0 . How should she be further evaluated and treated?

THE CLINICAL PROBLEM

Primary hyperparathyroidism is the most common cause of hypercalcemia and should be considered in any person with an elevated serum calcium level.¹ In the 1970s, the estimated prevalence of primary hyperparathyroidism ranged from 1 case per 1000 persons in the United States² to 4.3 cases per 1000 persons in Sweden.³ In Sweden, there was an estimated prevalence of 2.1 cases per 100 women between the ages of 55 and 75 years in the early 1990s.⁴ Data from the Rochester Epidemiological Project showed that the incidence of primary hyperparathyroidism increased sharply in the United States in July 1974, when the serum calcium level was included in the standard chemistry panel; from 1993 to 2001, the estimated incidence was approximately 22 cases per 100,000 persons per year.⁵ With increased detection by means of routine calcium screening, the clinical profile of primary hyperparathyroidism in Western countries has shifted from a symptomatic disease, characterized by hypercalcemic symptoms, nephrolithiasis, overt bone disease, and neuromuscular symptoms to one with subtle or no specific symptoms ("asymptomatic" primary hyperparathyroidism).⁶ In the developing world, the symptomatic variant still dominates.^{7,8}

The incidence of primary hyperparathyroidism peaks in the seventh decade. Most cases occur in women (74%), but the incidence is similar in men and women before 45 years of age.⁵

ETIOLOGIC FACTORS

Head and neck irradiation in childhood⁹ and long-term lithium therapy¹⁰ are associated with a greater prevalence of primary hyperparathyroidism. Primary hyperparathyroidism, which is most often caused by a single adenoma (80 to 85%) or four-gland hyperplasia (10 to 15%),¹ mainly occurs as a sporadic disease, but it may be part of a hereditary syndrome (e.g., multiple endocrine neoplasia types 1 and 2A) (Table 1).¹¹

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KEY CLINICAL POINTS

EVALUATION AND TREATMENT OF PRIMARY HYPERPARATHYROIDISM

- Primary hyperparathyroidism is the most common cause of hypercalcemia, affecting at least 1 in 1000 persons (more with increased age).
- Most patients with primary hyperparathyroidism are asymptomatic at diagnosis.
- An elevated or unexpectedly “normal” parathyroid hormone level simultaneous with an elevated albumin-adjusted calcium level generally is diagnostic of primary hyperparathyroidism.
- Neck imaging is not indicated for diagnosis, but it is useful for localization before planned parathyroidectomy.
- Parathyroidectomy should be recommended for patients with symptomatic primary hyperparathyroidism and for patients with asymptomatic primary hyperparathyroidism who meet criteria established by international guidelines, as well as those for whom surveillance is not feasible.
- Surveillance (including measurement of calcium levels and bone mineral density) is an option for patients with asymptomatic primary hyperparathyroidism, but monitoring is needed because disease progression may occur.

CLINICAL PRESENTATION

Classic symptoms and signs of primary hyperparathyroidism are rare today, but nephrolithiasis still occurs in 4 to 15% of cases.¹² Patients may have weakness, easy fatigability, anxiety, and cognitive impairment even when the level of serum calcium is modestly increased.⁶ Associated insulin resistance, hyperglycemia, and dyslipidemia (decreased levels of high-density lipoprotein cholesterol and increased levels of total triglycerides) have been reported, but it remains unclear how often these are attributable to the hyperparathyroidism and whether they are ameliorated by surgery.¹³⁻¹⁶ Hypertension is also common and, with sophisticated testing (which is not routinely performed), subtle cardiovascular changes (i.e., increased vascular stiffness and endothelial dysfunction) may be detected.^{6,17,18} Low bone mineral density, particularly at sites enriched in cortical bone (e.g., the distal third of the radius) is common.¹⁹ Cross-sectional studies show an increased rate of fractures among persons with primary hyperparathyroidism²⁰; in one prospective study, the rate of morphometric (but not clinical) vertebral fracture was increased among asymptomatic postmenopausal women with primary hyperparathyroidism, as compared with age-matched controls.²¹

Normocalcemic primary hyperparathyroidism (increased PTH concentration in the absence of hypercalcemia) has been recognized,²² typically among persons evaluated for low bone mineral density (whose assessment may include measure-

ment of both calcium and PTH). This diagnosis should be made only after all causes of secondary hyperparathyroidism have been ruled out.

NATURAL HISTORY

The natural history of primary hyperparathyroidism varies according to its severity. Symptomatic patients who do not undergo surgery usually have worsening disease (particularly recurrent nephrolithiasis).^{23,24} Conversely, long-term observational studies²³⁻²⁵ have shown stability up to 8 years in biochemical measures (serum calcium, PTH, creatinine, and urinary calcium) and in bone mineral density in the majority of asymptomatic patients, whose serum calcium level is typically within 1 mg per deciliter (0.25 mmol per liter) above the upper normal range. However, about one third of patients have worsening of hypercalcemia, hypercalciuria, and decreases in bone mineral density at cortical sites, with progression more likely among those with the longest follow-up²⁴ and those who are younger at study entry.²³ Short-term follow-up (1 to 3 years) of asymptomatic patients with mild primary hyperparathyroidism has indicated stability of markers of bone turnover, lipid and glucose levels, and echocardiographic indexes.²⁶⁻²⁸ The natural history of normocalcemic primary hyperparathyroidism is not known, but, in a longitudinal study with a mean follow-up of 3 years, hypercalcemia developed in 7 of 37 patients (19%).²⁹

The risk of death from cardiovascular causes is increased among patients with moderate-to-

Table 1. Hereditary States of Hyperparathyroidism.

Disorder	Responsible Gene	Pathogenic Mechanism	Associated Clinical Features
MEN type 1*	<i>MEN1, CDKN1B</i>	Loss-of-function mutation	Pituitary and gastroenteropancreatic tumors; less frequently, adrenal tumor, facial angiofibroma, collagenoma, and lipoma
MEN type 2A	<i>RET</i>	Gain-of-function mutation	Medullary thyroid cancer, pheochromocytoma, cutaneous lichen amyloidosis
Hyperparathyroidism– jaw tumor syndrome	<i>CDC73</i> (formerly known as <i>HRPT2</i>)	Loss-of-function mutation	Fibromas in the mandible or maxilla, renal and uterine tumors, increased rate of parathyroid carcinomas (15–20%)
Familial hypocalciuric hypercalcemia	<i>CASR</i>	Loss-of-function mutation	Rare pancreatitis, relative hypocalciuria (24-hr urinary calcium:creatinine ratio, <0.01)
Neonatal severe primary hyperparathyroidism	<i>CASR</i>	Loss-of-function mutation	Life-threatening condition with marked hypercalcemia, hypotonia, and respiratory distress
Familial isolated hyperparathyroidism	<i>MEN1, CDC73, CASR, CDKN1B</i>	Loss-of-function mutation	Lack of the specific features of the other syndromic forms

* Multiple endocrine neoplasia (MEN) type 1, a syndrome associated with a *CDKN1B* gene mutation, is also referred to as MEN type 4.¹¹

severe primary hyperparathyroidism^{1,17} and persists long after successful parathyroidectomy, suggesting that there may be irreversible cardiovascular damage.¹⁷ Most^{17,30,31} but not all³² studies suggest that patients with asymptomatic primary hyperparathyroidism do not share this risk.

STRATEGIES AND EVIDENCE

EVALUATION

The finding of hypercalcemia on routine biochemical testing or in the evaluation of postmenopausal women with osteoporosis is typically the initial clue to the diagnosis of primary hyperparathyroidism.^{1,6} The total serum calcium level, which combines both the free and albumin-bound components of circulating calcium, should be adjusted for the level of albumin as follows: corrected or adjusted total calcium = (measured total calcium in mg per deciliter) + $[0.8 \times (4.0 - \text{patient's serum albumin concentration in g per deciliter})]$. Measurement of ionized calcium may be useful in selected cases, such as in patients with hyperalbuminemia, thrombocytosis, Waldenström's macroglobulinemia, and myeloma³³; these patients may have elevated levels of total serum calcium, but normal levels of ionized serum calcium (artificial hypercalcemia).

Measurement of serum PTH is the next step in the evaluation of hypercalcemia. An elevated level of PTH (or a level that is in an unexpected "normal" range) simultaneous with an elevated calcium level generally indicates a diagnosis of primary hyperparathyroidism.¹ However, these

laboratory findings may also occur with lithium or thiazide use, tertiary hyperparathyroidism associated with end-stage renal failure, and familial hypocalciuric hypercalcemia, and a medical and family history should be obtained to assess these possibilities. The finding of a normal level of albumin-adjusted or ionized serum calcium and an elevated level of PTH in patients with no other causes of secondary hyperparathyroidism is consistent with normocalcemic primary hyperparathyroidism. A low or undetectable PTH level rules out primary hyperparathyroidism and raises the possibility of cancer-associated hypercalcemia,^{1,33} often mediated by PTH-related protein, which does not cross-react with the PTH assay. If the PTH level is elevated in a person with a known malignant condition, the most likely diagnosis is concomitant primary hyperparathyroidism; ectopic production of PTH from a tumor is extremely rare.¹

Once the diagnosis of primary hyperparathyroidism has been established, a familial form, accounting for about 5% of cases, should be considered. Young age (<30 years) at diagnosis; a family history of hypercalcemia, neuroendocrine tumors, or both; the presence of skin lesions associated with multiple endocrine neoplasia syndromes (Table 1); or the presence of all these factors increases the likelihood of familial primary hyperparathyroidism; in such cases, the level of serum calcium should be measured in all first-degree relatives. A palpable neck mass (which is not expected in primary hyperparathyroidism), markedly elevated levels of serum

Table 2. Guidelines for the Treatment of Asymptomatic Primary Hyperparathyroidism.

Variable	Criteria for Surgery*	Surveillance without Surgery
Serum calcium level	>1.0 mg/dl (0.25 mmol/liter) above upper limit of normal range	Annually
Creatinine clearance (calculated)†	Reduced to <60 ml/min	Annually
Bone mineral density	T score less than -2.5 at any site,‡ previous fragility fracture, or both	Every 1–2 yr (three sites)
Age	<50 yr	Not applicable

* Surgery should also be recommended for patients in whom surveillance is not feasible.

† The estimated glomerular filtration rate (milliliters per minute per 1.73 m² of body-surface area) should be calculated from the serum creatinine concentration, demographic characteristics (age, sex, and race or ethnic group), and other serum measurements (e.g., blood urea nitrogen and albumin concentrations) according to the following equation: $170 \times (\text{serum creatinine in mg per deciliter})^{-0.999} \times (\text{blood urea nitrogen in mg per deciliter})^{-0.170} \times (\text{serum albumin in g per deciliter})^{0.318} \times (\text{age in years})^{-0.176} \times (0.762 \text{ if patient is female}) \times (1.180 \text{ if patient is black})$. Equation is from Eastell et al.³⁵

‡ Sites were the lumbar spine, total hip, femoral neck, and distal third of the radius. According to the International Society for Clinical Densitometry, z scores instead of T scores should be used in evaluating bone mineral density in premenopausal women and men younger than 50 years of age.

calcium (>14 mg per deciliter [3.5 mmol per liter]) and PTH (3 to 10 times the upper limit of normal), or both, especially in men, suggest the possibility of parathyroid carcinoma, although this is rare (<1% of cases of primary hyperparathyroidism).³⁴

Laboratory testing should include assessment of renal function (Table 2)³⁵ and the level of serum 25-hydroxyvitamin D. Levels of 25-hydroxyvitamin D below 50 nmol per liter (20 ng per milliliter) are common, probably because of its increased conversion to 1,25-dihydroxyvitamin D and accelerated catabolism in patients with primary hyperparathyroidism,³⁶ and this may further aggravate the disease by increasing PTH secretion. The 24-hour urinary calcium and creatinine level should be measured to rule out familial hypocalciuric hypercalcemia; a calcium:creatinine clearance ratio below 0.01 suggests this diagnosis,³⁷ and hypercalcemia in one or more first-degree relatives also supports it. Sequencing the calcium-sensing receptor gene, which is mutated in familial hypocalciuric hypercalcemia, may be helpful when family screening is inconclusive. In selected cases (e.g., in young patients with a family history of a syndrome-associated tumor), genetic testing may be warranted to determine the cause of primary hyperparathyroidism and the risk of other tumors.¹¹

Renal ultrasonography is recommended if the history suggests nephrolithiasis, but it may also be considered in the absence of such a history to rule out kidney stones or nephrocalcinosis³⁵ (the

presence of which would alter management recommendations; see below). Renal ultrasonographic evaluations have shown nephrolithiasis in 7% of patients with asymptomatic primary hyperparathyroidism.³⁸ Bone mineral density should be measured at the lumbar spine, hip, and distal third of the forearm. PTH has a catabolic effect on cortical bone, and sites enriched in cortical bone are preferentially reduced.¹⁹ Indeed, most patients have a reduction of bone mineral density at the distal third of the forearm and relative preservation at the lumbar spine, with intermediate values at the hip; a small subgroup (15%) of patients may have vertebral osteopenia or osteoporosis.³⁹ Plain-film radiography of the skeleton is not recommended, except in rare cases of severe disease in which osteitis fibrosa cystica is suspected.

Neck imaging is not indicated for diagnosis, but it is useful for disease localization before planned parathyroidectomy (Fig. 1).¹ Sestamibi scanning and ultrasonography are used most commonly. The main advantage of sestamibi scanning is that it may localize ectopic parathyroid glands.

TREATMENT

Parathyroid Surgery

When intervention is indicated, the goal of treatment is to cure the disease by removing the abnormal parathyroid tissue. Parathyroidectomy should be recommended in all patients with symptomatic primary hyperparathyroidism. Pa-

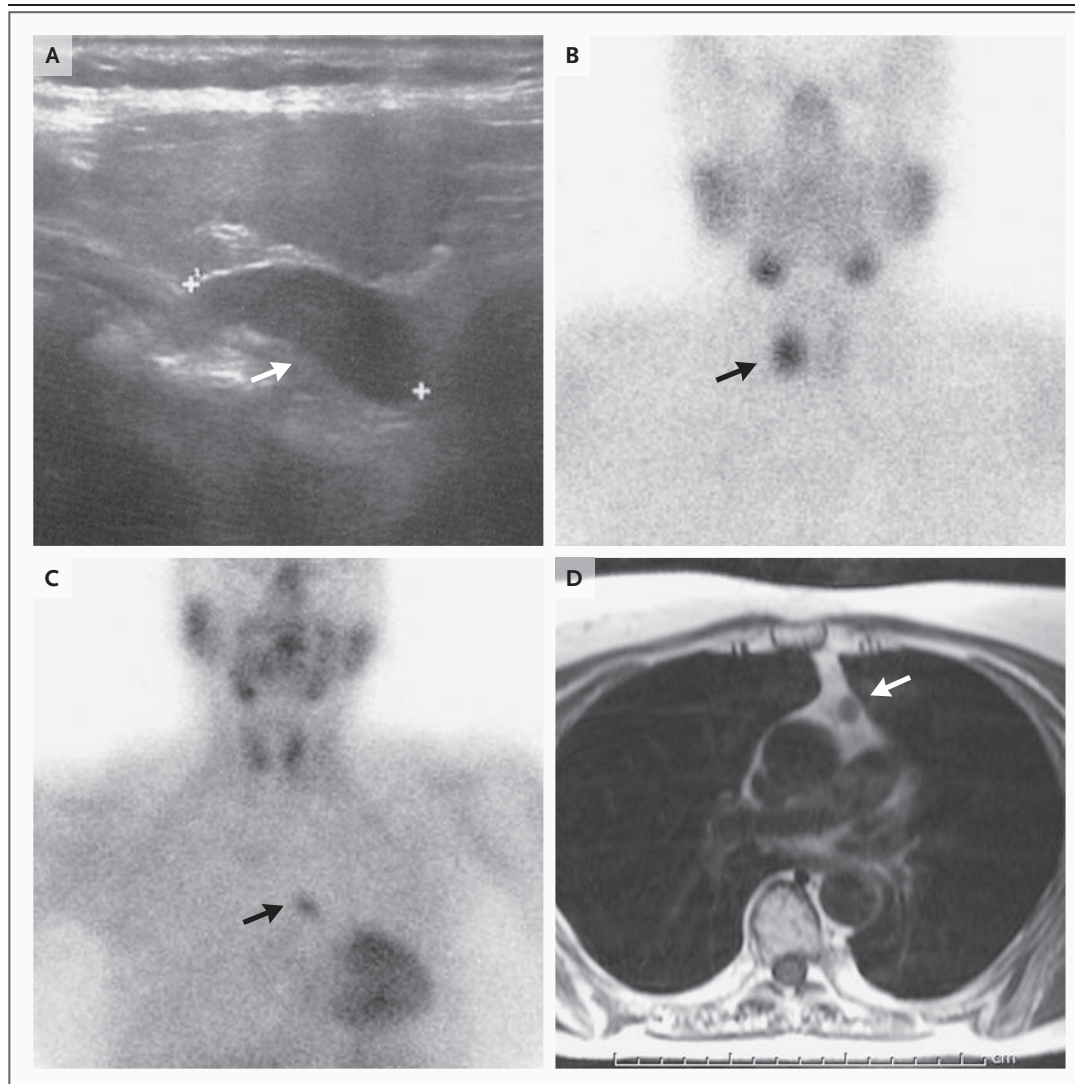


Figure 1. Parathyroid Imaging.

Panel A shows a longitudinal ultrasonographic image of the right thyroid lobe of the patient described in the vignette. An enlarged parathyroid gland appears homogeneously solid and markedly more hypoechoic than the adjacent thyroid tissue (arrow). Panel B shows a delayed-phase planar sestamibi scan indicating a marked uptake at the level of the right thyroid lobe, where the ultrasound localized the parathyroid lesion (arrow) in the patient described in the vignette. Panels C and D show a mediastinal parathyroid adenoma in a 65-year-old woman with primary hyperparathyroidism. In Panel C, a delayed-phase sestamibi scan shows a marked uptake at the level of the middle mediastinum (arrow). In Panel D, a magnetic resonance imaging scan (T_1 -weighted image) of the chest shows a lesion in the aortopulmonary window (arrow). The patient underwent a sternotomy, and a parathyroid adenoma was excised.

tients presenting with relatively mild hypercalcemia (serum calcium level <12 mg per deciliter [3 mmol per liter]) (the majority of patients with primary hyperparathyroidism) can proceed directly to surgery. In the rare patients with higher calcium levels, preoperative treatment is required with saline infusion, followed by loop diuretics, and intravenous bisphosphonates or calcimimet-

ics (cinacalcet) to reduce the serum calcium level and minimize the risk of complications associated with more severe hypercalcemia. These complications include hypovolemia, acid-base abnormalities, and cardiac-rhythm disturbances.

Parathyroidectomy should also be considered for some patients with asymptomatic primary hyperparathyroidism. According to the Third

International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism, surgery is recommended for patients meeting any of the criteria for surgery listed in Table 2, as well as those for whom surveillance is not feasible.⁴⁰ However, these are guidelines, not rules, and decisions should take into account patient preferences, the presence of coexisting conditions, and the expertise of available surgeons.

In experienced hands, parathyroidectomy is associated with a cure rate of 95 to 98% and a low rate (1 to 3%) of complications (laryngeal-nerve palsy and, less frequently, postoperative hypocalcemia). As compared with open procedures, minimally invasive approaches are associated with a shorter operating time, a more rapid postoperative recovery, and lower complication rates.^{41,42} Minimally invasive surgery is increasingly used, although it is generally not performed in patients with a large goiter or previous neck surgery. Intraoperative PTH monitoring may be helpful; a decrease of 50% or more in the PTH level 10 minutes after adenoma resection, as compared with the highest value before excision, suggests that all hyperfunctioning parathyroid tissue has been removed.⁴³ Histologic analysis usually shows a single, benign, chief-cell adenoma. When histologic findings are equivocal, molecular studies may help to identify parathyroid cancer.³⁴ Recurrence is rare in sporadic primary hyperparathyroidism, but the risk is higher in familial cases, unless total parathyroidectomy is performed. Successful surgery is followed by a prompt normalization of the PTH level and serum and urinary calcium levels and gradual increases in bone mineral density (up to 10%), mostly during the first few postoperative years at the lumbar spine and hip, and later at the distal radius.²⁴ Recurrence of nephrolithiasis is rare.⁴⁴ Hypertension generally persists after successful parathyroidectomy.¹⁷ Randomized trials showing short-term outcomes (1 to 3 years) suggest that surgery, as compared with surveillance, also may be of benefit for bone mineral density and quality of life in patients who do not meet the criteria for surgery.²⁶⁻²⁸

SURVEILLANCE

For patients who do not undergo parathyroidectomy, annual monitoring of serum calcium and creatinine levels and assessment of bone mineral density every 1 or 2 years is recommended (Table 2),⁴⁰ although data are lacking to inform appropri-

ate testing strategies and frequencies of follow-up. Maintenance of adequate levels of 25-hydroxyvitamin D (>50 nmol per liter [20 ng per milliliter]) and an adequate dietary calcium intake are recommended, since low vitamin D levels and low calcium intake may exacerbate parathyroid overactivity.⁴⁵

MEDICAL THERAPY

At present, there is no definitive medical therapy for primary hyperparathyroidism. However, treatment options are available and should be considered in patients who are not eligible for or are unwilling to undergo parathyroidectomy but in whom there is an indication to reduce the level of serum calcium, increase the bone mineral density, or both.

Placebo-controlled trials have shown improvement in bone mineral density in postmenopausal women with primary hyperparathyroidism and mild hypercalcemia who are treated with antiresorptive therapy. In one trial, estrogen therapy (conjugated estrogen at a dose of 0.625 mg plus medroxyprogesterone at a dose of 5 mg daily for 2 years) increased bone mineral density at the femoral neck and lumbar spine⁴⁶; however, long-term estrogen use is no longer recommended, given the associated cardiovascular and breast-cancer risks. In another study involving patients with mild disease, the bisphosphonate alendronate (at a dose of 10 mg daily for 2 years) reduced bone-turnover markers and increased bone mineral density at the lumbar spine and hip, but not at the distal radius⁴⁷; levels of serum calcium and PTH did not change significantly. No long-term data on the efficacy and safety of antiresorptive therapy in primary hyperparathyroidism are available.

For patients in whom bone mineral density is not low, but in whom the serum calcium level is more than 1 mg per deciliter above the normal range, cinacalcet may be considered. Cinacalcet is approved in Europe and the United States for the treatment of moderate-to-severe hypercalcemia in patients with primary hyperparathyroidism who are unable to undergo parathyroidectomy. It has been shown to decrease serum calcium levels across a broad range of severity in primary hyperparathyroidism.⁴⁸⁻⁵⁰ In clinical studies, normocalcemia was achieved in 70 to 100% of patients with asymptomatic primary hyperparathyroidism^{48,49} and in 28 to 68% of those with more severe disease.⁵⁰ However, PTH

levels decreased only modestly and generally remained elevated. In an uncontrolled study involving treatment for up to 5.5 years, bone mineral density did not change significantly at any site.⁴⁸ Cinacalcet is generally initiated at a dose of 30 mg once or twice daily, and the dose is adjusted according to the serum calcium level, with median doses of 60 mg daily in patients with asymptomatic primary hyperparathyroidism^{48,49} and 120 mg daily in patients with more severe primary hyperparathyroidism.⁵⁰ Once normocalcemia is achieved or the maximum tolerated dose is reached, the serum calcium level should be monitored every 2 to 3 months. Adverse events are generally mild or moderate. The most common events are headache and gastrointestinal symptoms; the rare event of hypocalcemia is managed by withdrawing medication for a few days and restarting at a lower dose.

AREAS OF UNCERTAINTY

Long-term data from randomized trials are lacking to compare outcomes of parathyroidectomy with conservative (nonsurgical) management in patients with asymptomatic primary hyperparathyroidism. The frequency and clinical significance of subtle cardiovascular and neurocognitive abnormalities in patients with otherwise asymptomatic primary hyperparathyroidism and the effects of parathyroidectomy on these manifestations warrant further study.

Longitudinal data are needed to better define the incidence of fractures in primary hyperparathyroidism before and after successful parathyroidectomy, to inform the natural history of normocalcemic primary hyperparathyroidism, and to assess the safety of the prolonged use of cinacalcet. It is uncertain whether a T score of -2.5 is the appropriate bone-mineral-density criterion for surgery in primary hyperparathyroidism. Moreover, the appropriate level of 25-hydroxyvitamin D in patients with primary hyperparathyroidism followed without parathyroidectomy and the effects of vitamin D supplementation on disease progression remain uncertain.

GUIDELINES

There are no formal guidelines from professional societies for the management of primary hyperparathyroidism. Updated international guidelines for the management of asymptomatic primary hyperparathyroidism were published in 2009.⁴⁰ The recommendations in this article are generally concordant with these guidelines.

CONCLUSIONS AND RECOMMENDATIONS

The woman described in the vignette has asymptomatic primary hyperparathyroidism associated with a bone mineral density T score of less than -2.5 at the distal third of the radius. Further evaluation should include assessment of the level of 25-hydroxyvitamin D and creatinine clearance. The ratio of urinary calcium to creatinine clearance is not in the range suggestive of familial hypocalciuric hypercalcemia (<0.01), and the family history does not suggest a familial form of primary hyperparathyroidism. Given the patient's bone mineral density T score, we would recommend parathyroidectomy, performed by means of a minimally invasive approach if available, if preoperative imaging studies localize the abnormal parathyroid gland or glands. If the patient declines surgery, we would advise adequate calcium intake (as for patients without primary hyperparathyroidism)⁴⁰ and vitamin D supplementation if serum levels of 25-hydroxyvitamin D are less than 20 ng per milliliter. To assess disease stability, serum calcium and creatinine levels should be followed yearly, and bone mineral density should be tested every 18 to 24 months, and we would strongly recommend parathyroidectomy if evidence of disease progression is detected.

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

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