Asymptomatic Primary Hyperparathyroidism

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A 60-year-old woman is noted incidentally to have a calcium level of 10.8 mg per deciliter (2.70 mmol per liter; normal range, 8.4 to 10.2 mg per deciliter [2.10 to 2.55 mmol per liter]). The parathyroid hormone level, as measured on immunoradiometric assay, is 84 pg per milliliter (normal range, 10 to 65). She has never had a kidney stone or a fracture, and she feels well. Her urinary calcium excretion is normal. Her bone density is within 0.5 SD of the peak bone mass at the lumbar spine and the hip and is 1.0 SD below the peak bone mass at the forearm. How should her case be managed?

For the first 40 years after its recognition as a clinical entity, primary hyperparathyroidism was a symptomatic disorder in which kidney stones and bone disease were common.\(^1\)\(^2\) Management was straightforward, since parathyroidectomy was always indicated. The advent of a multichannel biochemical screening test in the early 1970s ushered in the era of asymptomatic primary hyperparathyroidism, and the incidence of this disorder increased by a factor of four to five.\(^3\)\(^4\)

In patients with asymptomatic primary hyperparathyroidism, the serum calcium concentration is elevated, but usually only to within 1 mg per deciliter above the upper limit of normal (10.2 mg per deciliter). The parathyroid hormone level, measured by means of immunoradiometric assay, is usually 1.5 to 2.0 times the upper limit of normal (65 pg per milliliter), although it may be inappropriately “normal.” Hypophosphatemia and hyperchloremia, which were common among patients with symptomatic disease, are uncommon among patients with asymptomatic disease. The 24-hour urinary calcium excretion tends to be near the upper limit of normal.

Although radiography almost never shows skeletal involvement, bone densitometry typically does. As measured on dual-energy x-ray absorptiometry, the greatest reduction in bone density is at the distal third of the radius, a site composed predominantly of cortical bone that is vulnerable to the catabolic actions of parathyroid hormone. The hip and the lumbar spine, sites where bone becomes progressively more cancellous, show smaller reductions.\(^5\) This pattern of bone loss differs from the usual pattern of the early postmenopausal years, when cancellous bone of the lumbar spine is lost preferentially. But in estrogen-deficient postmenopausal women with primary hyperparathyroidism, bone density at the lumbar spine is generally well preserved, emphasizing a protective effect of parathyroid hormone against the loss of cancellous bone. Recent trials showing improved bone density at the lumbar spine in postmenopausal women with osteoporosis who were treated with intermittent low-dose parathyroid hormone have confirmed its anabolic potential.\(^6\) However, occasionally, patients with primary hyperparathyroidism do have bone loss at the lumbar spine.\(^7\)\(^8\)\(^9\)

Approximately 20 percent of patients are symptomatic, with kidney stones, overt bone disease, or proximal neuromuscular weakness.\(^10\)\(^11\) Some patients do report weakness,
easy fatigability, intellectual weariness, and even depression.12,13 Since these symptoms are nonspecific and hard to attribute to primary hyperparathyroidism in particular, they do not enter prominently into decisions regarding surgery, nor do they necessarily define patients as symptomatic. When the calcium level exceeds 12 mg per deciliter (3.0 mmol per liter), such nonspecific problems are more likely to be related to primary hyperparathyroidism.

A less common presentation of asymptomatic primary hyperparathyroidism is characterized by a normal serum calcium level but an elevated parathyroid hormone level. This condition is typically identified during an evaluation of skeletal health. The diagnosis is made when there is no apparent cause of secondary elevations of the parathyroid hormone level and the serum 25-hydroxyvitamin D level is not below the lower limit of the physiologically normal range (i.e., is above 20 ng per milliliter). This normocalcemic variant may represent the earliest manifestation of primary hyperparathyroidism.14

Although asymptomatic primary hyperparathyroidism commonly occurs in countries that use multichannel screening tests, symptomatic disease is common in other geographic areas, such as India, northeastern Brazil, and China, where access to multichannel screening is limited.15 In addition, the high prevalence of vitamin D deficiency in these countries may fuel the processes associated with overactivity of the parathyroid glands, leading to more cases of symptomatic disease.

### Strategies and Evidence

#### Diagnosis

Although there are clear advantages to measuring the concentration of ionized calcium rather than the total calcium concentration, most experts in the United States use the total serum calcium concentration, corrected for the patient’s albumin concentration (by adding 0.8 mg per deciliter to the total serum calcium value for every 1 g per deciliter below a serum albumin concentration of 4 g per deciliter). The corrected total serum calcium concentration is used because of the technical challenges involved in the accurate measurement of ionized calcium. The diagnosis of primary hyperparathyroidism is made on the basis of the combination of an elevated total serum calcium concentration and an elevated or inappropriately normal parathyroid hormone level.16

There are many causes of hypercalcemia, but few are associated with elevated levels of parathyroid hormone, and thus the differential diagnosis of hypercalcemia does not usually present difficulties. A newly introduced immunoradiometric assay for parathyroid hormone detects only the intact, full-length 84-amino-acid molecule.17 This more specific assay has the potential to be more clinically useful than the established immunoradiometric assay for parathyroid hormone, in which large fragments truncated at the N-terminal end are measured along with the full-length molecule.18

When the parathyroid hormone level is elevated in a patient with hypercalcemia, the differential diagnosis includes hyperparathyroidism due to thiazide diuretics or lithium, familial hypocalciuric hypercalcemia, and the tertiary hyperparathyroidism associated with end-stage renal disease. If the patient is taking a thiazide diuretic or lithium and it is considered to be safe to discontinue the use of the medication, then it should be withdrawn and the patient retested three months later. If the serum calcium concentration continues to be elevated, it can be concluded that the hypercalcemia is due to primary hyperparathyroidism. Familial hypocalciuric hypercalcemia is distinguished from primary hyperparathyroidism by a family history of mild hypercalcemia, a usual onset in young adulthood, and a ratio of urinary calcium to urinary creatinine of less than 0.01.19 Humoral hypercalcemia of malignancy should not be a consideration when the parathyroid hormone level is high, because the hypercalcemic agent in this condition, parathyroid hormone–related protein, is not detected by the immunoradiometric assay for parathyroid hormone. If the parathyroid hormone level is high in a patient with humoral hypercalcemia of malignancy, he or she is more likely to have concomitant primary hyperparathyroidism and cancer than to have a cancer that has produced authentic parathyroid hormone (a situation that is reported rarely).

### Natural History of Asymptomatic Primary Hyperparathyroidism Without Surgery

Management decisions about asymptomatic primary hyperparathyroidism require knowledge of its natural history. Most patients who do not meet the criteria for surgery (listed below) do well, with no evidence of progressive disease.20 In most patients who are followed without surgery, the average serum levels of calcium and parathyroid hormone do not change over a 10-year period. Average bone mass as measured by dual-energy x-ray absorptiometry...
outcomes after parathyroid surgery

Most adults with primary hyperparathyroidism (80 to 85 percent) have a single benign adenoma, whereas 15 to 20 percent have hyperplasia of all four parathyroid glands. Parathyroid cancer is exceedingly rare (found in less than 0.5 percent of patients with hyperparathyroidism).

Although the standard surgical approach is the exploration of all four parathyroid glands with the use of general anesthesia, an alternative approach is to perform the same four-gland operation with the use of local anesthesia. Another strategy is a unilateral operation in which the other gland on the side that harbors the adenoma is ascertained to be normal. Since multiple parathyroid adenomas are unusual, the presence of one normal parathyroid gland is considered by some to be sufficient evidence of single-gland disease.

When performed by an expert parathyroid surgeon, these approaches are successful more than 90 percent of the time. However, since not all surgeons are experts and the parathyroid glands are notoriously variable in their location, preoperative localization has become popular in recent years. Imaging with technetium-labeled sestamibi, with or without single-photon-emission computed tomography, is a preferred method, although there are other approaches to localization (ultrasonography, computed tomography, and magnetic resonance imaging). Most experts consider preoperative imaging to be mandatory for patients who have had previous neck surgery, but its use in patients without such a history remains controversial.

Preoperative parathyroid imaging is required for all patients who are to undergo minimally invasive parathyroidectomy, a procedure that is directed only at the site where the abnormal parathyroid gland has been visualized. After the removal of the parathyroid gland that is presumed to be abnormal, a sample of peripheral blood is obtained intraoperatively for a rapid parathyroid hormone assay. If the level decreases by more than 50 percent after resection, the gland that has been removed is considered to be the sole source of overactive parathyroid tissue, and the operation is terminated. If the parathyroid hormone level does not decrease by more than 50 percent, the operation is extended to a more traditional one in a search for other overactive parathyroid tissue. There is controversy over the use of minimally invasive parathyroidectomy, since it may miss another overactive gland (a second adenoma or four-gland hyperplasia) whose activity is relatively suppressed when a larger, more dominant gland is present.

Complications of parathyroidectomy include injury to the recurrent laryngeal nerve or hypoparathyroidism, both of which are very uncommon if the procedure is performed by an expert parathyroid surgeon. Symptomatic hypocalcemia may occur in the postoperative period in patients with more severe primary hyperparathyroidism (termed “hungry bone syndrome”), but it is rare in patients with mild disease.

After the removal of the parathyroid adenoma or multiple overactive glands, the serum and urinary calcium concentrations return to normal. The rate of recurrence of kidney stones has been reduced by more than 90 percent after parathyroid surgery in some series. Over a period of three to four years, bone density improves, with the lumbar spine and hip regions typically showing increases of 12 to 14 percent without the need to resort to antiresorptive therapy. In patients with vertebral osteopenia, increases in bone density at these sites can approach 20 percent. The density of the distal third of the radius changes little, if at all. Although some reports have suggested that patients feel better in terms of a number of subjective variables after surgery, more rigorous quantitative assessment of quality-of-life measures after surgery is still needed.

Areas of Uncertainty

Long-term Risks

The long-term risks associated with living with chronic hypercalcemia are unknown. In a population-based study from the United States, mild,
asymptomatic primary hyperparathyroidism was not associated with increased overall mortality, although mortality was increased among patients in the highest quartile of serum calcium concentrations.\textsuperscript{29} Whereas classic primary hyperparathyroidism has been linked to cardiovascular disorders (hypertension), gastrointestinal disorders (peptic ulcer disease), and metabolic disorders (diabetes mellitus), it is not clear whether these individual associations are causal.\textsuperscript{13} Studies from Europe, however, indicate that patients with primary hyperparathyroidism may have increased cardiovascular risk, rates of lipid disorders, rates of glucose intolerance, and mortality.\textsuperscript{30-34}

The incidence of fracture among patients with primary hyperparathyroidism is unknown. Although the risk of fracture has been reported to be increased at all sites,\textsuperscript{33} an increased risk of vertebral fracture is a surprising finding, since most patients have relatively well preserved vertebral bone density. An increased incidence of forearm fractures is more consistent with the finding of reduced bone density at that site. However, even this risk is uncertain, because it is now known that parathyroid hormone may increase the cross-sectional area of bone and therefore strengthen it, even if the bone density appears to be reduced.\textsuperscript{36}

**MEDICAL THERAPY**

There is considerable interest in the development of a safe, medical approach to asymptomatic primary hyperparathyroidism. The use of estrogen therapy in postmenopausal women with primary hyperparathyroidism is associated with small reductions (of 0.5 to 1 mg per deciliter) in the serum calcium concentration and increases in bone density, along with stable parathyroid hormone levels.\textsuperscript{37} However, risks associated with estrogen use have been well publicized recently.\textsuperscript{38} In addition, doses higher than the current standard have been most consistently associated with beneficial effects in primary hyperparathyroidism, although some positive studies have used lower doses.\textsuperscript{39} Raloxifene, a selective estrogen-receptor modulator, is a potential alternative. In a short-term (eight-week) trial involving 18 postmenopausal women, raloxifene was associated with a statistically significant, although small (0.5 mg per deciliter), reduction in the serum calcium concentration and in the levels of markers of bone turnover.\textsuperscript{40}

Since primary hyperparathyroidism is characterized by high bone turnover, potent bisphosphonates are another therapeutic option. In recent clinical trials involving small numbers of patients with primary hyperparathyroidism, the use of alendronate has resulted in significant increases (of 4 to 6 percent) in vertebral bone density.\textsuperscript{41,42} Serum calcium and parathyroid hormone levels do not change significantly.

The calcimimetic drug cinacalcet has been investigated in patients with primary hyperparathyroidism.\textsuperscript{43} By increasing the affinity of the parathyroid-cell calcium receptor for extracellular calcium, this agent leads to an increase in intracellular calcium and a subsequent reduction in parathyroid hormone secretion. This action, in turn, reduces the serum calcium level. Clinical trials have demonstrated prolonged normalization (lasting up to three years) of the serum calcium level\textsuperscript{44} but no change in bone density as measured on dual-energy x-ray absorptiometry. There are no data regarding the incidence of fractures with this agent or any other medical therapy in patients with primary hyperparathyroidism. More information is required about all these potential medical approaches to asymptomatic primary hyperparathyroidism before evidence-based recommendations can be made regarding their use in this disorder.

**CALCIUM AND VITAMIN D INTAKE**

Although it is prudent for patients to refrain from the ingestion of more calcium than is recommended for adults (1200 to 1500 mg per day), it is also important not to restrict calcium intake too much (to less than 750 mg per day). Calcium-poor diets may fuel processes associated with excessive secretion of parathyroid hormone. Many patients with asymptomatic primary hyperparathyroidism have levels of 25-hydroxyvitamin D that are at the lower end of the normal range or frankly low,\textsuperscript{45} and a low level of supplementation, achievable with a multivitamin (400 IU of vitamin D daily), is reasonable. Patients should be advised to be cautious about using higher doses of vitamin D, because hypercalcemia and hypercalciuria can develop and worsen quickly. They should also be advised to maintain adequate fluid intake, because dehydration can exacerbate hypercalcemia.

**OTHER UNCERTAINTIES**

Data are lacking regarding the natural history of the recently recognized normocalcemic variant of primary hyperparathyroidism. In addition, more research is needed on possible neuropsychological, cardiovascular, and metabolic manifestations of mild hyperparathyroidism. The roles of newer as-
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says for parathyroid hormone, newer imaging methods, and different surgical approaches require further study.

GUIDELINES

In 2002, the National Institutes of Health (NIH) Workshop on Asymptomatic Primary Hyperparathyroidism revisited key issues related to the management of this condition that had previously been addressed in the 1990 NIH Consensus Development Conference. A panel convened after the workshop recommended new management guidelines that relate specifically to the asymptomatic form of the disease. The current guidelines for surgery are compared with the 1990 guidelines in Table 1. In the new guidelines, the serum calcium concentration above which surgery is recommended has been lowered to 1 mg per deciliter above the upper limit of normal, because the panel judged that levels that are consistently higher than this are associated with greater risks of complications. The recommendation that bone densitometry be performed at three sites (the lumbar spine, the hip, and the distal third of the radius) reflects the fact that this disease can affect all bones and that the radius is particularly vulnerable. The use of the T score for bone mineral density and the guideline recommending surgery if the T score is less than −2.5 are consistent with the definition of osteoporosis established by the World Health Organization.

Some patients with asymptomatic primary hyperparathyroidism do not meet any of these criteria for surgery. For these patients, a conservative approach including monitoring (as outlined in Table 2) is considered to be an appropriate and safe alternative.

Table 1. Comparison of Old and New Criteria for Parathyroid Surgery in Patients with Asymptomatic Primary Hyperparathyroidism.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>1990 Guidelines</th>
<th>2002 Guidelines</th>
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<tbody>
<tr>
<td>Serum calcium concentration</td>
<td>1.0–1.6 mg/dl above upper limit of normal</td>
<td>1.0 mg/dl above upper limit of normal</td>
</tr>
<tr>
<td>24-Hr urinary calcium excretion</td>
<td>&gt;400 mg</td>
<td>&gt;400 mg</td>
</tr>
<tr>
<td>Reduction in creatinine clearance</td>
<td>30%</td>
<td>30%</td>
</tr>
<tr>
<td>Bone mineral density</td>
<td>Z score below −2.0 in the forearm</td>
<td>T score below −2.5 at any site</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;50 Yr</td>
<td>&lt;50 Yr</td>
</tr>
</tbody>
</table>

* Data are from Bilezikian et al.

Table 2. Comparison of Old and New Management Guidelines for Monitoring Patients with Asymptomatic Primary Hyperparathyroidism Who Do Not Undergo Parathyroid Surgery.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Recommended Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum calcium level</td>
<td>Every 6 mo</td>
</tr>
<tr>
<td>24-Hr urinary calcium excretion</td>
<td>Annual</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>Annual</td>
</tr>
<tr>
<td>Serum creatinine concentration</td>
<td>Annual</td>
</tr>
<tr>
<td>Bone density</td>
<td>Annual, at all 3 sites</td>
</tr>
<tr>
<td>Abdominal radiography</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

* Data are from Bilezikian et al.

REFERENCES

5. Silverberg SJ, Shane E, De La Cruz L, et

CONCLUSIONS AND RECOMMENDATIONS

Many patients with asymptomatic primary hyperparathyroidism will not require surgery. On the basis of long-term follow-up in patients as well as expert opinion, accepted indications for surgery include a serum calcium concentration that is at least 1 mg per deciliter above the upper limit of normal, marked hypercalcemia (urinary calcium excretion of more than 400 mg per day), reduced bone density (a T score of less than −2.5 at any site), and an age of less than 50 years. For patients who do not meet any of these criteria, such as the patient described in the vignette, monitoring with semianual measurement of serum calcium and annual measurement of bone mass is recommended. Patients should be encouraged to maintain an active lifestyle, with normal intakes of calcium and vitamin D.

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