ABSTRACT
• **Objective:** To review new developments in the diagnosis and management of primary hyperparathyroidism.
• **Methods:** Review of the literature.
• **Results:** Primary hyperparathyroidism is one of the most common endocrine disorders, especially among postmenopausal women. Patients with hypercalcemia can be diagnosed with primary hyperparathyroidism in the setting of elevated or inappropriately normal parathyroid hormone (PTH) levels. A newer presentation of primary hyperparathyroidism has been described, normocalcemic primary hyperparathyroidism, in which patients have normal total and ionized serum calcium concentrations and consistently elevated PTH levels, excluding secondary etiologies of hyperparathyroidism. Most patients with primary hyperparathyroidism present asymptptomatically, although decreased bone density at the distal 1/3 radius site is usually noted at the time of diagnosis.
• **Conclusion:** Patients with symptomatic primary hyperparathyroidism and those with asymptomatic disease who meet criteria for surgery should be advised to have surgical removal of the abnormal parathyroid gland(s). Those who do not meet criteria for surgery can be managed nonoperatively with surveillance by biochemical and densitometric measurements. Pharmacologic options are available for those who meet surgical criteria but either refuse surgery or are not deemed suitable for surgery.

Over the past 40 years, the clinical presentation of primary hyperparathyroidism has changed from a disorder with overt symptomatology to one that presents most commonly asymptptomatically. It is discovered most often in the context of a biochemical screening test in which the discovery of hypercalcemia is a surprise. Investigation of this more modern phenotype of primary hyperparathyroidism has revealed new insights into the diagnosis, management, and natural history of primary hyperparathyroidism. This review will cover the new developments in the field.

**CASE STUDY**

**Initial Presentation**

A 72-year-old Hispanic woman with a history of hypertension and morbid obesity was referred to an endocrinologist for hypercalcemia noted on routine laboratory evaluation.

**History**

Her past medical and surgical history was otherwise significant for hyperlipidemia, hypothyroidism, depression, gastroesophageal reflux disease, and chronic headache. She denied a history of fracture or nephrolithiasis. Review of systems was significant only for chronic constipation. Her medications included amlodipine, telmisartan, ezetimibe-simvastatin, levothyroxine, citalopram, and lansoprazole. The patient was born and raised in the Dominican Republic; social history was otherwise unremarkable. Family history was significant for leukemia and breast cancer but negative for parathyroid disease or other endocrine disorders.

**Physical Examination, Laboratory, and Radiographic Evaluation**

Examination was significant for a body mass index of 47.5 kg/m², absence of thyromegaly or nodules, absence of neck masses, absence of kyphosis or vertebral tenderness. Her most recent laboratory testing prior to evaluation was significant for a serum calcium level of 10.8 mg/dL (reference range [rr], 8.6–10.2), ionized calcium of 1.53 mM/L (rr, 1.12–1.32), parathyroid hormone (PTH) 104 pg/mL (rr, 10–65),
25-hydroxyvitamin D 28 ng/mL (rr, 30–100), albumin 4.0 g/dL (rr, 3.5–5.5), creatinine 0.8 mg/dL (rr, 0.50–0.90), phosphorus 2.9 mg/dL (rr, 2.5–4.3), and total alkaline phosphatase 102 U/L (rr, 33–96). A bone mineral density was obtained and demonstrated T-scores of −0.3 at the lumbar spine, −0.3 at the femoral neck, +1.2 at the total hip, and −1.5 at the distal 1/3 radius. 24-hour urine calcium excretion was obtained and was noted to be 240 mg (rr, 50–250).

**What is the epidemiology of primary hyperparathyroidism? What are the biochemical and clinical features?**

Maintenance of sufficient levels of calcium is required for many physiologic processes, among them normal neuromuscular function and bone mineralization. PTH produced by the parathyroid glands is an important regulator of serum calcium through its effects on bone, the kidney, and intestines. In primary hyperparathyroidism, one or more of the parathyroid glands become enlarged and overactive. Primary hyperparathyroidism is, thus, a disorder characterized by elevated levels of PTH and tradionally by hypercalcemia. Primary hyperparathyroidism is one of the most common endocrine disorders, with an estimated prevalence in the United States between 1 and 2 per 1000. Most patients present after the age of 45 years; women are affected more often than men by 3:1. Prior to the advent of the multichannel autoanalyzer in the 1970s, classical primary hyperparathyroidism presented usually as a symptomatic disorder [1–3]. The original description more than 70 years ago as a disease of “bones, stones and groans” was apt. Overt skeletal disease was readily recognized by radiographic features of osteitis fibrosa cystica: “salt and pepper” degranulation of the skull, subperiosteal bone resorption of the distal phalanges, brown tumors, loss of distal clavicular appearance and bone cysts [4]. With serum calcium values now routinely available as a biochemical screening test result, the clinical profile of primary hyperparathyroidism has evolved into a disorder that presents most commonly in an asymptomatic fashion. In these patients, the discovery of hypercalcemia is made incidentally [5].

The typical biochemical features of primary hyperparathyroidism are shown in Table 1 [6,7]. Serum calcium is usually within 1.0 mg/dL (0.25 mmol/L) above the upper limit of normal. Serum phosphorus is usually in the low normal range, although 25% of patients will have levels that are frankly low. The average vitamin D level, as measured by 25-hydroxyvitamin D, is low, averaging 20 ng/mL. Vitamin D deficiency is due in part to the effects of PTH to facilitate the conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D [8]. Up to 25% of patients will have frankly elevated 1,25-dihydroxyvitamin D levels. Total alkaline phosphatase activity and more specific markers of bone turnover such as osteocalcin and serum and urine N- and C-telopeptide levels, are all usually in the high normal range. 24-hour urinary calcium excretion is typically in the upper range of normal, with a 40% incidence of frank hypercalciuria [9]. While the incidence of hypercalciuria has not changed over the past 60 years, the incidence of renal stone disease has fallen markedly. This speaks to an interesting point, namely that in primary hyperparathyroidism, hypercalciuria is not a risk factor for kidney stones [7].

Despite the fact that most patients are discovered incidentally, and x-rays rarely show classical findings of primary hyperparathyroidism, bone mass is typically reduced when it is measured by dual energy x-ray absorptiometry (DXA). Primary hyperparathyroidism tends to preferentially affect cortical (also known as compact) bone, the bone that forms the outer shell, or envelope, of bones. The densitometric profile of primary hyperparathyroidism shows reductions at the distal 1/3 forearm, a site composed primarily of cortical bone [5,6]. High-resolution imaging of the radius [10] and histomorphometric analysis of bone biopsies [11] have confirmed this finding. In contrast, the lumbar spine, a site composed primarily of trabecular bone (also known as spongy bone), tends to be preserved [12]. In estrogen-deficient, postmenopausal women without primary hyperparathyroidism, the lumbar spine site is at greatest risk for bone loss, making the observation that trabecular bone is preserved in these individuals even more noteworthy. This observation, namely preservation of trabecular bone in primary hyperparathyroidism, offered clues to the osteoanabolic potential of PTH [13]. The administration of low-dose, intermittent PTH revealed this osteoanabolic property and led to the development of PTH as a treatment for osteoporosis [14–16]. Information about fracture risk in primary hyperparathyroidism is inconsistent due to lack of rigorous prospective data and the inclusion of populations with varying disease severity [17–20]. In a study by Vignali et al [21] stratifying by disease
severity, both symptomatic and asymptomatic patients with primary hyperparathyroidism had an increased risk of vertebral fracture. However, those asymptomatic individuals who did not meet surgical criteria did not show an increased risk in comparison to a control population.

While nephrolithiasis is still the most common complication of primary hyperparathyroidism, the incidence has fallen to 15% to 20%, much lower than estimates of about 60% in the era prior to the autoanalyzer [5,22]. Other renal manifestations of primary hyperparathyroidism include hypercalciuria and nephrocalcinosis. The frequency of nephrocalcinosis is unknown. An unexplained reduction in the creatinine clearance is also believed to be a potential renal manifestation of primary hyperparathyroidism. Walker et al [23] showed that a creatinine clearance < 60 cc/min is associated with worse indices of skeletal disease as determined by bone biopsy in comparison to subjects with primary hyperparathyroidism whose renal function is normal.

Nontraditional manifestations of primary hyperparathyroidism, primarily potential effects on the cardiovascular system and neurocognitive function, are areas of active research. In mild primary hyperparathyroidism, subtle evidence for cardiovascular dysfunction, including altered endovascular function [24] and increased vascular stiffness, has been reported [25,26], but the clinical relevance of these findings are not clear. Nonspecific neurocognitive features, such as weakness, easy fatigability, depression, cognitive impairment, anxiety, and sleep disturbance, have been difficult to identify as direct manifestations of primary hyperparathyroidism. Associated improvement in quality of life and psychological functioning following successful parathyroidectomy has not been a consistent finding among the 4 groups that have studied this problem recently [27–30].

• What are other presentations of primary hyperparathyroidism?

**Normocalcemic Primary Hyperparathyroidism**

A newer clinical presentation of primary hyperparathyroidism has been described over the past decade, characterized by normal total and ionized serum calcium concentrations and consistently elevated PTH levels [31–34]. Patients with normocalcemic primary hyperparathyroidism have no obvious causes for secondary elevations of PTH, such as renal disease or vitamin D deficiency. Identification of this new phenotype of primary hyperparathyroidism is consistent with a biphasic time course of the clinical development of primary hyperparathyroidism [33]. During the first phase, PTH levels are elevated but the serum calcium is normal. Until recently, this phase would not be recognized clinically because PTH levels were not drawn in the context of a normal serum calcium concentration. The second phase, when overt hypercalcemia becomes apparent, is the stage of the disease that has characterized most cohorts of primary hyperparathyroidism until recently. The discovery of this putative first phase of primary hyperparathyroidism, when the serum calcium is normal, would appear to be due to the fact that many osteoporosis and metabolic bone disease units now measure PTH routinely in the evaluation of bone loss. Reports of normocalcemic primary hyperparathyroid-

---

Table 1. Biochemical Indices in 57 Patients with Asymptomatic Primary Hyperparathyroidism

<table>
<thead>
<tr>
<th>Index</th>
<th>Baseline Values*</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum calcium, mg/dL</td>
<td>10.5 ± 0.1</td>
<td>8.4–10.2</td>
</tr>
<tr>
<td>Serum parathyroid hormone, pg/mL</td>
<td>116 ± 7</td>
<td>10–65</td>
</tr>
<tr>
<td>Urinary calcium, mg/dL</td>
<td>236 ± 17</td>
<td>&lt; 300</td>
</tr>
<tr>
<td>Alkaline phosphatase, U/L</td>
<td>98 ± 6</td>
<td>&lt; 100</td>
</tr>
<tr>
<td>Serum 25-hydroxyvitamin D, ng/mL</td>
<td>21 ± 1</td>
<td>&gt; 30†</td>
</tr>
<tr>
<td>Serum 1,25-dihydroxyvitamin D, pg/mL</td>
<td>57 ± 2</td>
<td>15–60</td>
</tr>
</tbody>
</table>

Reprinted from reference 6.

*Values are mean ± SEM.

†Many experts consider 25-hydroxyvitamin D levels > 30 ng/mL to indicate sufficiency.
Primary Hyperparathyroidism

Table 2. Genetic Hyperparathyroid Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Main Gene</th>
<th>Associated Features</th>
<th>Parathyroid Pathology</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial hypocalciuric hypercalcemia</td>
<td>CASR</td>
<td>Hypocalciuria, rare pancreatitis</td>
<td>None (normal)</td>
<td>No parathyroidectomy</td>
</tr>
<tr>
<td>Neonatal severe hyperparathyroidism</td>
<td>CASR</td>
<td>Life-threatening hypercalcemia</td>
<td>Early, 4 large glands</td>
<td>Urgent total parathyroidectomy</td>
</tr>
<tr>
<td>Multiple endocrine neoplasia type 1</td>
<td>MEN1</td>
<td>Pituitary and pancreas tumors</td>
<td>Multiglandular</td>
<td>Subtotal parathyroidectomy</td>
</tr>
<tr>
<td>Multiple endocrine neoplasia type 2A</td>
<td>RET</td>
<td>Pheochromocytoma and medullary thyroid cancer</td>
<td>Multiglandular</td>
<td>Subtotal parathyroidectomy</td>
</tr>
<tr>
<td>Hyperparathyroidism-jaw tumor syndrome</td>
<td>HRPT2</td>
<td>Fibromas in the mandible or the maxilla, parathyroid cancer</td>
<td>Parathyroid carcinoma (20%)</td>
<td>Surgical resection of cancer if it develops</td>
</tr>
<tr>
<td>Familial isolated hyperparathyroidism</td>
<td>Unknown</td>
<td>None</td>
<td>Multiglandular</td>
<td>Parathyroidectomy based on severity</td>
</tr>
</tbody>
</table>

Note: All entries represent typical features of a broad spectrum of disease.

Is there a putative “early” phase of primary hyperparathyroidism in which subjects were under evaluation for bone loss? For example, of the 37 individuals who were described with normocalcemic primary hyperparathyroidism at Columbia University Medical Center [35], 57% had osteoporosis by BMD, 11% had documented fragility fractures, and 14% had nephrolithiasis. The observation that subjects with this putative “early” phase of primary hyperparathyroidism have evidence for skeletal involvement, not different from hypercalcemic cohorts, raises the possibility that there is another population of normocalcemic subjects with primary hyperparathyroidism who would not have evidence for skeletal involvement if they were identified from a general population. Studies are in progress to identify the other form of normocalcemic primary hyperparathyroidism [36,37].

Primary Hyperparathyroidism in the Developing World

Interestingly, while primary hyperparathyroidism in the developed world has become a disorder of mild, asymptomatic hypercalcemia, the clinical picture of primary hyperparathyroidism in the developing world, in which vitamin D deficiency is more common and biochemical screening tests are not routinely performed, remains a disease with classic signs and symptoms, including osteitis fibrosa cystica as well as other skeletal and renal complications. Primary hyperparathyroidism in the setting of vitamin D deficiency is associated with a more severe phenotype [7], with larger adenomas, higher serum calcium, parathyroid hormone, and alkaline phosphatase levels, lower bone mineral density, and higher fracture rates [38–42].

What is the etiology of primary hyperparathyroidism?

In primary hyperparathyroidism, clones of abnormal parathyroid cells alter the “set-point” sensitivity of the parathyroid gland to calcium and increase the mass of parathyroid tissue. PTH is higher for any given extracellular concentration of calcium [43]. A single gland adenoma is the most common cause of primary hyperparathyroidism, accounting for approximately 80% of cases. Multiple adenomas are reported in 2% to 4% of patients, and 4-gland hyperplasia in 10% to 15%. Very rarely, primary hyperparathyroidism can present as a malignant carcinoma, but the incidence is less than 0.5% among the hyperparathyroid population [39,40]. There are no clinical features that distinguish patients with single versus multiglandular disease. However, younger patients (< 40 years), particularly those with a personal or family history of a multiple endocrine neoplasia (MEN) syndrome, are more likely to have multiglandular disease. Occasionally, parathyroid adenomas will be found in unexpected anatomic locations due to embryonal migration patterns of parathyroid tissue. The most common sites for ectopic adenomas are within the thyroid gland, the superior mediastinum, and within the thymus [2].
Although most patients have sporadic disease, hereditary syndromes in which primary hyperparathyroidism is prominent include MEN types 1 and 2A, hyperparathyroidism-jaw tumor syndrome, neonatal severe primary hyperparathyroidism, and familial isolated hyperparathyroidism (Table 2) [3,44,45].

Ionizing radiation to the head and neck has been associated with the development of primary hyperparathyroidism many decades after exposure [46–48]. This usual etiology is dependent, in part, on dose and time from exposure. The absolute risk with therapeutic doses of radiation remains quite low, < 1% at 35 years and only about 5% after 50 years of follow-up [49]. There are case reports and case series suggesting an association with radioactive iodine therapy for the treatment of benign and malignant thyroid conditions [50–52], although a prospective cohort study failed to demonstrate an increased incidence of parathyroid disease after radioactive iodine treatment, with a mean follow-up time of 21 years [53].

• How is the diagnosis made?

The 2 principal causes of hypercalcemia are primary hyperparathyroidism and malignancy. In the outpatient setting, primary hyperparathyroidism is much more common. Patients with hypercalcemia due to malignancy usually have clinically established advanced cancer. The clinical setting distinguishing between these 2 most common etiologies of hypercalcemia is supported further by measurement of the PTH level. It is frankly elevated in about 75% to 80% of patients with primary hyperparathyroidism, and inappropriately normal in the remaining subjects. In contrast, PTH is typically undetectable in patients with malignancy-associated hypercalcemia. An undetectable PTH level in a hypercalcemic individual, however, does not indicate a malignancy because most of the other causes of hypercalcemia, a long list indeed, are associated with suppressed levels of PTH [3].

If the PTH is elevated, the disorders that could be mistaken for primary hyperparathyroidism are small in number. They include familial hypocalciuric hypercalcemia [54] and medications, specifically thiazide diuretics [55] and lithium [56]. Very rarely a malignant tumor has been reported to secrete ectopic PTH, as opposed to the more commonly reported PTH-related peptide (PTHrP) [57–59].

Familial hypocalciuric hypercalcemia (FHH) is a rare, benign disorder caused by loss of function mutations in the calcium sensing receptor (CASR) gene. A diagnosis of FHH can be suspected by a family history of FHH or a 24-hour urine calcium collection showing very low values for calcium excretion on a normal calcium diet. In FHH, the 24-hour urinary calcium is well under 100 mg/day and calcium to creatinine clearance ratio is less than 0.01 mmol/L [60]. If the calcium-to-creatinine clearance ratio is greater than 0.02, FHH becomes very unlikely. CASR gene analysis for a single point mutation identified in FHH can be considered in a patient with a calcium to creatinine clearance ratio < 0.02 [61]. It is important to distinguish FHH from primary hyperparathyroidism because the parathyroid glands are normal in FHH and surgery is never indicated. It is also important to remember that FHH is a rare disorder while primary hyperparathyroidism is a common one. Moreover, since PTH is a calcium-conserving hormone, by facilitating renal tubular calcium reabsorption, a low calcium-to-creatinine clearance ratio does not establish the diagnosis of FHH.

Thiazide diuretics can be associated with hypercalcemia due to a number a factors such as thiazide-associated reduced urinary calcium excretion, a metabolic alkalosis resulting in a pH-dependent increase in protein-bound calcium, and increased calcium absorption from the intestines [62,63]. Discontinuation or substitution of the thiazide can be considered if there are no contraindications, with subsequent retesting of calcium and PTH in 3 to 6 months. Most hypercalcemic patients taking thiazide diuretics will ultimately be diagnosed with primary hyperparathyroidism [64]. Lithium decreases sensitivity to calcium within the parathyroid gland and may also reduce urinary calcium excretion [56,65]. Short-term use of lithium might be associated with reversible hypercalcemia but, like thiazide diuretic use, most patients on lithium will have been on lithium for many years when hypercalcemia is discovered [59]. It is not easy to discontinue lithium, as one can often stop or substitute for a thiazide diuretic. The diagnosis of primary hyperparathyroidism in these individuals is usually clear. If they meet criteria for surgery and there are no contraindications to surgery, most experts will proceed to obtain preoperatively localization of the putative parathyroid adenoma.

Hypercalcemia, the classical biochemical hallmark of primary hyperparathyroidism, is not always present in traditional primary hyperparathyroidism. Although
patients are hypercalcemic most of the time, the serum calcium level can be normal during the course of monitoring. The “normal” serum calcium in these traditionally hypercalcemic individuals is usually in the upper normal range. These individuals do not have “normocalcemic primary hyperparathyroidism” in which the serum calcium is always normal (see above). The diagnostic criteria for normocalcemic primary hyperparathyroidism include consistently normal albumin-adjusted total serum calcium and normal ionized calcium. Additionally, secondary causes of an elevated PTH level must be excluded:

- Vitamin D deficiency: There is controversy surrounding the precise threshold value for 25-hydroxyvitamin that leads to an increase in PTH. The Institute of Medicine report [66] concluded that there was insufficient evidence that levels of 25-hydroxyvitamin D ≥ 20 ng/mL are regularly associated with increases in PTH levels in population sampling. However, these studies are confounded by the lack of any prospective data tracking PTH on an individual level as the 25-hydroxyvitamin D level is increased. The diagnosis of normocalcemic primary hyperparathyroidism can be made with greater certainty when the 25-hydroxyvitamin D level is greater than 30 ng/mL. In addition, normocalcemic patients with hyperparathyroidism will occasionally become hypercalcemic when 25-hydroxyvitamin D levels are raised to over 30 ng/mL. Ensuring vitamin D sufficiency, therefore, may unmask the latent hypercalcemic state of primary hyperparathyroidism.

- Reduced creatinine clearance. Martinez et al [67–69] demonstrated that PTH begins to rise with a glomerular filtration rate < 60 cc/min.

- Use of thiazide diuretics and lithium

- Hypercalciuria

- Gastrointestinal malabsorption

What is the natural history of primary hyperparathyroidism?

Natural History Without Surgery

Two large, prospective cohorts have helped to define the natural history of the disease and the criteria that are used to determine which patients with asymptomatic primary hyperparathyroidism are candidates for curative surgery. Rao et al [33] followed 80 asymptomatic patients for up to 11 years, during which time there was no worsening of biochemical or densitometric indices. Silverberg et al [5] followed a cohort of 101 asymptomatic patients up to 10 years, showing that while most patients did well, approximately 25% of these patients did progress, with age as the only predictor of disease progression. Patients younger than 50 years of age were approximately 3 times as likely to have disease progression. Rubin et al [6] reported the 15-year follow-up study of these patients, finding that disease progression over that longer time period increased to 37% of the cohort. Particularly noteworthy was accelerated bone loss at the distal 1/3 radius and femoral neck between years 10 and 15.

The natural history of normocalcemic primary hyperparathyroidism is less well defined. In the cohort from Columbia University Medical Center [35], 40% developed further signs of primary hyperparathyroidism during a mean follow-up period of 3.1 ± 0.3 years. Hypercalcemia developed in 19% of these individuals. The subjects who became hypercalcemic tended to be older, have higher baseline serum calcium levels, and higher baseline urinary calcium excretion.

Natural History With Surgery

In the cohort studied by the group at Columbia University Medical Center, 59 patients who underwent successful parathyroid surgery experienced densitometric gains at 5, 10, and 15 years, respectively, of 9%, 6%, and 12% at the lumbar spine; 1%, 7% and 10% at the femoral neck; and 4%, 8%, and 7% at the distal radius. Randomized controlled trials of surgery versus observation [27,28,30] have also shown increased bone density at the hip and/or lumbar spine. These studies failed to show a change at the distal 1/3 radius site, which is understandable given the short-term follow-up. Using high-resolution peripheral quantitative computed tomography (HRpQCT), subjects 1 year after parathyroidectomy [70] showed increases in cortical and trabecular volumetric bone density in both the radius and tibia along with improvements in bone microarchitecture and estimated strength in the radius.

How is primary hyperparathyroidism managed?

Surgical Management

Parathyroidectomy is the only curative option for patients with primary hyperparathyroidism. Patients with
symptomatic primary hyperparathyroidism, manifested by kidney stones, fracture or marked hypercalcemia, should be managed surgically with removal of the abnormal parathyroid gland(s). Even with refinements to the surgical procedure over the last decade, it remains exceedingly important that highly experienced surgeons with interest in, and aptitude for, parathyroid surgery perform the procedure [71]. The standard operation for parathyroidectomy used to be a full neck exploration with identification of all 4 parathyroid glands, with the rationale being that 15% to 20% of patients with sporadic primary hyperparathyroidism will have 4-gland hyperplasia. Recent advances in preoperative imaging modalities and in intraoperative monitoring of PTH levels have led to the minimally invasive parathyroidectomy, which can be performed under local anesthesia [72,73]. The minimally invasive operation consists of identification and removal of the abnormal tissue without visualization of the other glands by the surgeon. Before and after the adenoma is removed, an intraoperative PTH level is obtained to confirm that the resected gland was the only source of excess PTH [74]. The abnormal tissue removed is considered to be the entirety of abnormal parathyroid tissue if the intraoperative PTH level falls by greater than 50% to a level into the normal range within 10 minutes after removal of the adenoma. If these criteria are not met, the operation is extended to an exploration of other sites where abnormal parathyroid tissue may be found. Success rates for parathyroid surgery with the minimally invasive procedure are over 90%, similar to the rates obtained with the classical 4-gland exploration [72]. The advantages of the minimally invasive procedure include its shorter length of time and much more rapid recovery in comparison to general anesthesia. In many centers, the operation is performed on an ambulatory basis without need for overnight observation.

In the case of parathyroid hyperplasia, options include subtotal parathyroidectomy (removal of 3.5 glands) or total parathyroidectomy with immediate autotransplantation of parathyroid tissue into the forearm. Should hyperparathyroidism recur, the forearm site provides easy access to the transplanted tissue. Cryopreservation facilities are necessary for autotransplantation in case the initial graft does not take. This approach is often used in cases of familial hyperparathyroidism in which 4-gland disease is most common [75,76].

Preoperative localization studies are necessary in preparation for any parathyroid surgery. The most common localization studies include neck ultrasound, computed tomography (CT) and radionuclide imaging (i.e., sestamibi). The sensitivity and specificity of each modality vary among institutions. Ultrasound has the advantages of low cost and ability to identify co-existing thyroid pathology. The sensitivity ranges from 42% to 82% depending on the operator, although the specificity is approximately 90% [77]. Sestamibi can be useful in the identification of ectopic parathyroid tissue and has a sensitivity approaching 90% for single adenomas, with decreased sensitivity for multiple lesions [78]. If the patient is not taking thyroid hormone, double-labeling with 123I and 99T sestamibi is preferred because the thyroid image generated by the 123I can be compute-subtracted from the image obtained by 99T sestamibi. Four-dimensional CT has also proven to be very successful in

---

**Table 3. Guidelines for the Treatment of Patients with Asymptomatic Primary Hyperparathyroidism**

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Surgical Criteria*</th>
<th>Medical Surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum calcium</td>
<td>1.0 mg/dL (0.25 mmol/L) &gt; upper limit of normal</td>
<td>Annually</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>Reduced to &lt; 60 cc/min (calculated)</td>
<td>Annually</td>
</tr>
<tr>
<td>Bone mineral density†</td>
<td>T-score &lt; –2.5 at any site‡ and/or previous fragility fracture</td>
<td>Every 1–2 years (3 sites)</td>
</tr>
<tr>
<td>Age</td>
<td>&lt; 50 years</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*Surgery is also indicated in patients for whom medical surveillance is neither desired nor possible.
†Consistent with the position established by the International Society for Clinical Densitometry, the use of Z-scores instead of T-scores is recommended in evaluating bone mineral density in premenopausal women and men younger than 50 years.
‡Lumbar spine, total hip, femoral neck or 1/3 radius.

Reprinted from reference 80.
identifying abnormal parathyroid tissue. Other localization approaches include magnetic resonance imaging and positron emission tomography. Arteriography and selective venous sampling may be needed in patients with persistent or recurrent disease in whom the noninvasive studies were unable to localize the lesion [79].

The Third International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism in 2008 [80] defined guidelines for the management of asymptomatic primary hyperparathyroidism (Table 3). Surgical management in asymptomatic patients should be considered in those with end-organ effects (osteoporosis at any site, creatinine clearance < 60 cc/min) or a higher likelihood of disease progression (age < 50 years, serum calcium > 1.0 mg/dL above the upper limit of normal). Marked hypercalciumia, a surgical indication in previous consensus conferences, was removed from the most current guidelines because urinary calcium has not been shown in primary hyperparathyroidism to be a risk factor for kidney stones [7].

**Medical Management**

Patients who do not meet surgical criteria can be observed with annual serum calcium, calculated creatinine clearance, and either annual or biannual bone densitometry (Table 3) [80]. Patients should be referred for parathyroid resection if they develop an indication for surgery during the follow-up period. While not part of guidelines, renal imaging with abdominal x-ray, ultrasonography, or CT can be considered in order to rule out renal involvement in subjects with no known history of kidney stones. Whether this approach to detecting renal calcifications should be part of conservative monitoring is a matter of clinical judgment. Patients found to have or to develop renal calcifications (nephrolithiasis or nephrocalcinosis) would become surgical candidates.

Patients with primary hyperparathyroidism and vitamin D deficiency present a particularly challenging dilemma due to the potential risk of worsening hypercalcemia with vitamin D supplementation. Moreover, patients with vitamin D deficiency may be at greater risk for developing hypocalcemia due to “hungry bone” syndrome following parathyroidectomy. A few published studies have focused upon the use of relatively high doses of vitamin D [81–84]. These studies show that vitamin D supplementation in primary hyperparathyroidism seems to be well tolerated and does not lead, in general, to worsening hypercalcemia or hypercalciumia.

The reports, however, also demonstrate the importance of careful monitoring. The optimal management of vitamin D deficiency is unknown, although most experts would recommend supplementation of 400 to 1000 IU daily and close monitoring of serum and urine calcium. More aggressive repletion of vitamin D deficiency can be considered post-parathyroidectomy to prevent “hungry bone” syndrome. Clinical trials are ongoing to determine optimal management of vitamin D deficiency in primary hyperparathyroidism (NCT00674154, NCT01306656, NCT01329666).

Patients who are not surgical candidates, refuse parathyroidectomy, or those with refractory primary hyperparathyroidism following surgery can be considered for medical therapy. Cinacalcet, a calcimimetic, is the only approved medical therapy for primary hyperparathyroidism in the United States, indicated for the treatment of severe hypercalcemia. Cinacalcet is an allosteric modulator of the calcium-sensing receptor that increases its sensitivity to extracellular calcium ions [85]. In a double-blind, randomized, 52-week placebo-controlled trial of 78 patients [86], cinacalcet was shown to significantly lower or normalize serum calcium and PTH levels in subjects with primary hyperparathyroidism. Serum phosphate was increased. Bone mineral density was unchanged. Cinacalcet was well tolerated, with the most common adverse effects being nausea and headache. The open-label 4.5-year extension of this trial [87] continued to show efficacy of cinacalcet. In primary hyperparathyroidism, most patients can be well controlled on a daily dose of 30 mg, although the official recommendation is to start with a twice daily dosing regimen. It is very uncommon for patients with primary hyperparathyroidism to require more than a twice daily dosing regimen. Conversely, in parathyroid cancer, much larger doses may be required, up to a maximum of 90 mg 4 times daily. Such high doses are poorly tolerated.

Antiresorptive therapeutic approaches have also been used in patients with primary hyperparathyroidism. In small studies, hormone replacement therapy [88–92], raloxifene [93,94], and bisphosphonates, with alendronate being the most studied [95–98], have all been shown to reduce bone turnover. Estrogen and raloxifene reduce the serum calcium concentration. Alendronate increases bone mineral density. However, there are no data on fracture efficacy with any of these therapies. An ongoing trial is investigating use of denosumab, a monoclonal antibody against receptor activator of
nuclear factor kappa B ligand (RANKL), in postmenopausal women with primary hyperparathyroidism (NCT01558115).

- What are considerations for the approach to normocalcemic primary hyperparathyroidism?

At the time of the National Institutes of Health Consensus Conference in 2008, the expert panel concluded that the guidelines for the hypercalcemic form of primary hyperparathyroidism could not be applied to normocalcemic primary hyperparathyroidism since so little was known about this variant. Our approach is to monitor patients with normocalcemic primary hyperparathyroidism similarly to the way we monitor patients with asymptomatic hypercalcemic primary hyperparathyroidism, with annual serum calcium, PTH, and bone mineral density. If the disease evolves into the hypercalcemic form, the guidelines from the Third International Workshop can then be followed [80]. Progression of the disease in other respects, such as worsening bone density, a fracture, or a kidney stone, would signal a more proactive surgical approach to the disease, even if patients continue to remain normocalcemic.

Case Follow-up

The patient was monitored for 5 years with stable annual serum calcium and PTH values and biannual bone mineral density evaluation. Serum calcium subsequently began to rise and was measured consistently in the 11.2–11.6 mg/dL range. Due to the rise in serum calcium to greater than 1 mg/dL above the normal range, parathyroidectomy was discussed with the patient. Parathyroid sestamibi demonstrated increased radiotracer uptake in the region of the inferior pole of the right thyroid gland, most consistent with a parathyroid adenoma. The patient was referred to an endocrine surgeon for minimally invasive parathyroidectomy. A 0.47-g right lower parathyroid was removed, with intraoperative PTH declining from 244 to 25 pg/mL within 10 minutes. Pathology was consistent with a parathyroid adenoma. She has now been followed 1 year postoperatively with normal serum calcium and PTH values.

CONCLUSION

Prior to the advent of the multichannel autoanalyzer in the 1970s, classical primary hyperparathyroidism commonly presented with marked hypercalcemia and symptomatic bone or stone disease. This presentation shifted 40 years ago to a disorder characterized by mild hypercalcemia without classical symptomatic features. We appear to have entered a third era in the history of this disease in which patients are now being discovered with normocalcemic primary hyperparathyroidism, defined by normal total and ionized serum calcium concentrations but with PTH levels that are consistently elevated. Our knowledge of normocalcemic primary hyperparathyroidism remains incomplete and further studies are required to further define the disorder. Patients with symptomatic disease or those who meet surgical criteria should be managed with parathyroid resection. Patients with asymptomatic primary hyperparathyroidism who do not meet criteria for surgery can be managed with annual surveillance of biochemical and densitometric indices.

Corresponding author: Natalie E. Cusano, MD, Columbia University College of Physicians and Surgeons, Division of Medicine, 630 West 168th St., PH 8W-864, New York, NY 10032, nc2433@columbia.edu.

Funding/support: This work was supported in part by National Institutes of Health grants DK52333 and DK095944.

Financial disclosures: Dr. Bilezikian is a consultant for Eli Lilly, NPS Pharmaceuticals, Merck, Warner-Chilcott, GSK, and Amgen, and receives research support from NPS Pharmaceuticals and Amgen.

REFERENCES

Primary Hyperparathyroidism


72. Udelson R, Lin Z, Donovan P. The superiority of mini-


