The Parathyroid Glands and Hyperparathyroidism: II

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I. INTRODUCTION

This manual is the second of a 2-part review on the parathyroid glands and hyperparathyroidism. The second part focuses on diagnosis and surgical treatment of hyperparathyroidism. A case patient is presented to illustrate important principles in the management of patients with hyperparathyroidism. The first part focused on embryology, anatomy, histology, and cell physiology of the parathyroid glands (Hospital Physician General Surgery Board Review Manual, Volume 6, Part 4).

II. CASE PATIENT 1

PRESENTATION

A 57-year-old man is found to have hypercalcemia on blood work obtained before a laparoscopic cholecystectomy for symptomatic cholelithiasis. His medical history is pertinent for a known hiatal hernia, hypertension, gout, hypercholesterolemia, and peptic ulcer disease. He denies any history of bone problems, kidney stones, pancreatitis, neuromuscular or behavioral abnormalities, or head or neck irradiation. There is no family history of thyroid, parathyroid, pituitary, pancreatic, or adrenal diseases. In addition to his cholecystectomy, he has previously undergone left knee surgery for a fractured patella.

Physical examination reveals a blood pressure of 128/78 mm Hg and heart rate of 100 bpm. He has no palpable neck masses, and the rest of his physical examination is unremarkable. Laboratory studies reveal a serum calcium of 12.3 mg/dL, serum phosphorus of 2.3 mg/dL, chloride level of 101 mEq/L, alkaline phosphatase level of 88 IU/L, and intact parathyroid hormone (PTH) level of 113 pg/mL (normal, 10 to 65 pg/mL).

• What is the most likely cause of patient 1’s hypercalcemia?

DISCUSSION

Primary Hyperparathyroidism

Primary hyperparathyroidism is one of the most common causes of hypercalcemia, accounting for 50% to 60% of cases diagnosed in the ambulatory setting and up to 27% diagnosed in the hospital. Primary hyperparathyroidism and malignancy account for 80% to 90% of all causes of hypercalcemia, although many other uncommon causes do exist (Table 1). Automated laboratory methods introduced in the late 1960s and early 1970s led to a dramatic increase in the recognition of this disorder. Approximately 100,000 people are newly
diagnosed with primary hyperparathyroidism each year in the United States. The condition affects women 2 to 3 times more often than men and occurs most commonly in postmenopausal women 50 to 60 years of age. The incidence of primary hyperparathyroidism also increases with age.

- What are the signs and symptoms of hyperparathyroidism?
- What laboratory tests are used to make a diagnosis?

**DISCUSSION**

**Clinical Presentation**

The spectrum of presenting symptoms has changed since primary hyperparathyroidism was first described in the 1930s. Patients rarely present with the classic skeletal manifestations and are less likely to have nephrolithiasis. Instead, most patients with hyperparathyroidism are diagnosed because of hypercalcemia detected from routine blood testing. Although they may appear asymptomatic, on questioning most patients admit to vague, nonspecific symptoms such as fatigue, muscle weakness, malaise, constipation, or depression.

Potential symptoms and associated metabolic conditions of hyperparathyroidism are extensive (Table 2). Skeletal manifestations include subperiosteal erosion, commonly involving the radial aspects of the second and third phalanges and distal clavicles; bone cyst formation; generalized demineralization; osteoporosis; and pathologic fractures. Less than 20% of patients with hyperparathyroidism have an abnormality demonstrable on plain radiographs of the skeleton.

Nephrolithiasis is the most frequent metabolic complication of the disease, occurring in 15% to 20% of patients. In addition, approximately 2% to 5% of patients with kidney stones have primary hyperparathyroidism. Other renal manifestations include asymptomatic hypercalcuria, nephrocalcinosis, and reduced creatinine clearance. Hypercalcuria—defined as a 24-hour urinary calcium concentration greater than 250 mg—occurs when the filtered load of calcium exceeds the resorbing capacity of the kidney. Nephrocalcinosis (calcium precipitation in the renal parenchyma) may be further associated with renal tubular dysfunction and impaired filtration.

Various other clinical symptoms are associated with primary hyperparathyroidism, such as gastrointestinal symptoms, a wide range of psychiatric symptoms, joint manifestations related to gout or pseudogout, rare dermatologic manifestations, and nonspecific neuromuscular symptoms (Table 2). Patients with hyperparathyroidism show an increased prevalence of hypertension.

**Table 1. Differential Diagnosis of Hypercalcemia**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperparathyroidism</td>
<td>Primary</td>
</tr>
<tr>
<td></td>
<td>Tertiary (occurs as a result of autonomous parathyroid function that develops in patients with longstanding secondary hyperparathyroidism, usually from chronic renal failure. It also refers to hyperparathyroidism that develops after renal transplantation)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Tumor metastases to bone</td>
</tr>
<tr>
<td></td>
<td>Pseudohyperparathyroidism (secretion of PTH-related peptide by renal cell carcinoma, squamous cell carcinoma of the lung, carcinoma of the urinary bladder)</td>
</tr>
<tr>
<td></td>
<td>Hematologic malignancies (multiple myeloma, lymphoma, leukemia)</td>
</tr>
<tr>
<td>Other endocrine disorders</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism</td>
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<tr>
<td></td>
<td>Adrenal insufficiency</td>
</tr>
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<td></td>
<td>Pheochromocytoma</td>
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<td></td>
<td>Vipoma</td>
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<tr>
<td></td>
<td>Acromegaly</td>
</tr>
<tr>
<td>Granulomatous diseases</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td></td>
<td>Sarcoïdiosis</td>
</tr>
<tr>
<td></td>
<td>Fungal infection</td>
</tr>
<tr>
<td></td>
<td>Leprosy</td>
</tr>
<tr>
<td>Exogenous agents</td>
<td>Calcium</td>
</tr>
<tr>
<td></td>
<td>Vitamin D</td>
</tr>
<tr>
<td></td>
<td>Vitamin A</td>
</tr>
<tr>
<td></td>
<td>Thiazide diuretics</td>
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<tr>
<td></td>
<td>Lithium</td>
</tr>
<tr>
<td></td>
<td>Milk alkali</td>
</tr>
<tr>
<td>Immobilization</td>
<td></td>
</tr>
<tr>
<td>Paget's disease</td>
<td></td>
</tr>
<tr>
<td>Familial hypocalciuric hypercalcemia</td>
<td>(an autosomal dominant disorder characterized by hypercalcemia, hypocalciuria, none of the complications of hypercalcemia, and a urinary calcium clearance less than 0.010 mmol/24 hr)</td>
</tr>
</tbody>
</table>

PTH = parathyroid hormone.
and a number of cardiovascular consequences (including left ventricular hypertrophy) may develop from the disorder.\textsuperscript{7} Untreated hyperparathyroidism can reduce a patient’s survival by approximately 10% when compared with expected values.\textsuperscript{5} This increased death rate is primarily the result of cardiovascular disease and less commonly of malignancy or renal failure.\textsuperscript{6–10} Further, disease duration seems to affect survival rates because the risk of death is increased in patients with higher serum calcium levels and larger adenomas.\textsuperscript{11,12} In patients with hyperparathyroidism, reduced survival can be reversed by parathyroidectomy.\textsuperscript{12}

Approximately 1.6% to 3.2% of patients with primary hyperparathyroidism present with acute hypercalcemic crisis, which usually manifests as a serum calcium level greater than 15 mg/dL and an altered mental status with progressive lethargy, confusion, stupor, or coma.\textsuperscript{13,14} Symptoms may also include weakness, nausea, vomiting, dehydration, cardiac arrhythmias, and a palpable tumor in the neck. In addition, patients in hypercalcemic crisis are more likely to present with osteitis fibrosa cystica, pancreatitis, and renal disease. If untreated, these patients may experience rapid deterioration in cerebral and renal function, multisystem organ failure, and death.

In most cases of hyperparathyroidism, the patient’s physical examination is unremarkable. Less than 5% of patients with the disease have a palpable tumor in the neck, which is more common in patients with parathyroid carcinoma or hypercalcemic crisis. Rare cases of hyperparathyroidism have been manifested by band keratopathy, which involves calcium phosphate deposition in the cornea that can be seen by slit-lamp examination.

When a patient presents with hypercalcemia, a diagnosis of hyperparathyroidism is made by documenting an elevated intact serum PTH level using immunoradiometric or chemiluminescence assay. In rare instances, PTH levels may be within the normal range but are always inappropriately elevated relative to the serum calcium level in patients with hyperparathyroidism. The intact PTH assays have no cross-reactivity with PTH-related polypeptide, which is elevated in certain malignancies known to cause pseudohyperparathyroidism. In the past, this cross-reactivity was a problem in different types of PTH assays. Hypercalcemia caused by conditions other than hyperparathyroidism should show PTH concentrations in low or undetectable amounts, with the exception of lithium-associated hyperparathyroidism or familial hypercalciuric hypercalcemia.

In rare circumstances, patients with primary hyperparathyroidism may have intermittent hypercalcemia or may even be normocalcemic. One study suggested that up to 25% of Scandinavian patients with primary hyperparathyroidism may have a serum calcium level within the upper half of the normal range.\textsuperscript{15} Normocalcemic

<table>
<thead>
<tr>
<th>System Conditions</th>
<th>Symptoms</th>
<th>Metabolic Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skeletal</td>
<td>Bone pain</td>
<td>Osteitis fibrosa cystica</td>
</tr>
<tr>
<td></td>
<td>Pathologic fractures</td>
<td>Osteopenia</td>
</tr>
<tr>
<td></td>
<td>Joint pain</td>
<td>Osteoporosis</td>
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<tr>
<td></td>
<td>Joint swelling</td>
<td>Gout</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pseudogout</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperuricemia</td>
</tr>
<tr>
<td>Renal</td>
<td>Colic</td>
<td>Nephrolithiasis</td>
</tr>
<tr>
<td></td>
<td>Hematuria</td>
<td>Nephrocacinosis</td>
</tr>
<tr>
<td></td>
<td>Polyuria</td>
<td>Hypercalciuria</td>
</tr>
<tr>
<td></td>
<td>Polydipsia</td>
<td>Reduced creatinine clearance</td>
</tr>
<tr>
<td></td>
<td>Nocturia</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Constipation</td>
<td>Peptic ulcer disease</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td></td>
</tr>
<tr>
<td>Psychiatric</td>
<td>Lethargy</td>
<td>Depression</td>
</tr>
<tr>
<td></td>
<td>Memory loss</td>
<td>Psychosis</td>
</tr>
<tr>
<td></td>
<td>Confusion</td>
<td>Coma</td>
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<td></td>
<td>Hallucinations</td>
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<tr>
<td></td>
<td>Delusions</td>
<td></td>
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<tr>
<td>Neuromuscular</td>
<td>Fatigue</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Muscle weakness</td>
<td></td>
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<tr>
<td></td>
<td>Malaise</td>
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<tr>
<td>Cardiovascular</td>
<td>Hypertension</td>
<td></td>
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<tr>
<td></td>
<td>Left ventricular hypertrophy</td>
<td></td>
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<tr>
<td></td>
<td>Heart block</td>
<td></td>
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<tr>
<td></td>
<td>Cardiac calcifications</td>
<td></td>
</tr>
<tr>
<td>Dermatologic</td>
<td>Brittle nails</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pruritus</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Clinical Manifestations of Primary Hyperparathyroidism

The Parathyroid Glands and Hyperparathyroidism: II
hyperparathyroidism should be suspected in patients with normal serum calcium levels who have symptoms or complications of hyperparathyroidism. Most of these cases are detected as a result of stone disease and to a lesser extent osteoporosis or other skeletal manifestations. Normocalcemic hyperparathyroidism may result from vitamin D deficiency, excess phosphate intake, low physiologic calcium set point, pancreatitis, or hypomagnesemia or hypermagnesemia.

In addition, patients with primary hyperparathyroidism may have a low or low-normal serum phosphorus level, a high or high-normal serum chloride level, and mild metabolic acidosis. These changes occur because PTH has an inhibitory effect on phosphorus and bicarbonate reabsorption in the renal tubule. As bicarbonate excretion increases, more chloride is reabsorbed with sodium in order to maintain electroneutrality. A chloride-to-phosphorus ratio of greater than 33:1 is consistent with a diagnosis of hyperparathyroidism. Before the advent of accurate PTH assays, this ratio was used to diagnose the disease. Patients with hyperparathyroidism may also have elevated alkaline phosphatase levels and hyperuricemia.

III. PATHOLOGY IN HYPERPARATHYROIDISM

DIAGNOSIS AND FURTHER TESTING

Patient 1 is diagnosed with sporadic primary hyperparathyroidism and undergoes a technetium-99m-sestamibi scan (Tc-99m-sestamibi) to localize the abnormal parathyroid tissue. Using a gamma camera, images of the neck and upper chest are obtained at 15 minutes and 2 hours after injection. No abnormality is seen in the thyroid gland region. Visualization of the right subclavian vein is achieved on immediate and delayed images. A focus of radioactivity in a right retrosternal position is consistent with an ectopic parathyroid adenoma (Figure 1). On the basis of this finding, surgical exploration is begun on the right side of the neck.

- What is the most likely pathology for patient 1?
- What are the best methods of detecting abnormal parathyroid glands?

DISCUSSION

The most common pathologies of hyperparathyroidism are a solitary adenoma (occurring in about 80% of patients), 4-gland hyperplasia (15% of patients), double adenoma (4%), and carcinoma (1%).

Most patients with sporadic hyperparathyroidism have a single adenoma, whereas those with a familial disorder usually have multiglandular disease. Individual hyperplastic parathyroid glands typically vary in size. Double adenomas are more commonly seen in patients older than 60 years. Parathyroid cancer is diagnosed on the basis of capsular or local invasion; metastases to lymph nodes or distant sites such as lungs, liver, or bone; or development of local recurrence after definitive surgical therapy.

Preoperative Parathyroid Localization

In patients who have undergone previous parathyroid exploration, preoperative imaging studies should be used to localize abnormal parathyroid tissue. Confirming the location of an abnormal parathyroid gland, usually through 2 noninvasive imaging techniques, helps to minimize dissection and reduce operative morbidity. Ultrasound, Tc-99m-sestamibi scintigraphy, computed tomography (CT), and magnetic resonance imaging (MRI) are most commonly used in preoperative parathyroid localization. Ultrasound is best used to identify a juxtapathyroidal, intrathyroidal, or ectopic parathyroid adenoma high in the neck (Figure 2); CT and MRI are most valuable for identifying ectopic parathyroid tissue in the mediastinum (Figure 3). These studies have a sensitivity of about 60% to 70%. The sensitivity of Tc-99m-sestamibi scintigraphy, however, has been reported to be 80% to 90%. Because of this increased sensitivity, imaging with Tc-99m-sestamibi should be the initial procedure for parathyroid localization.
Tc-99m-sestamibi scanning is performed using a dual-phase technique: 25 mCi of Tc-99m-sestamibi is administered, after which early and delayed images of the neck and thorax are obtained with a gamma camera (15 minutes and 2 hours after injection, respectively). These studies include both anterior-posterior views and oblique views, which help to distinguish a parathyroid adenoma that is posterior to the thyroid gland from a thyroid nodule or an intrathyroidal parathyroid adenoma. Tc-99m-sestamibi scintigraphy may be combined with single-photon emission CT for 3-dimensional imaging; however, this is rarely necessary because an experienced surgeon can find an abnormal parathyroid gland. Like all noninvasive imaging studies, Tc-99m-sestamibi lacks sensitivity to detect multiglandular disease. In patients with persistent or recurrent hyperparathyroidism, arteriography and selective venous sampling for intact PTH can be performed when noninvasive imaging studies are unsuccessful in localizing abnormal parathyroid tissue.

Routine preoperative parathyroid localization before initial neck exploration has generally not been advocated. However, this technique may be valuable in identifying ectopic parathyroid glands and in focusing the surgeon’s attention to the site of pathology, which may avoid unnecessary dissection and reduce operative time. The usefulness of preoperative localization is shown for patient 1: a retrosternal parathyroid adenoma is identified by a preoperative sestamibi scan; later, this adenoma is demonstrable intraoperatively only after the thymus is progressively pulled up from the chest. Identification of a rare ectopic parathyroid adenoma in the aortopulmonary window before initial surgical exploration has also been reported.

The aortopulmonary window was resected through a median sternotomy, sparing the patient an unnecessary neck exploration. With current techniques, an ectopic parathyroid adenoma in the chest can be resected thoracoscopically.

Tc-99m-sestamibi scintigraphy often is not used before initial exploration because the procedure is believed to be too expensive. At our institution, however, the cost of a simple dual-phase Tc-99m-sestamibi scan is comparable to that of an ultrasound examination or 15 minutes of operating room time. Thus, a preoperative Tc-99m-sestamibi scan can be effective if it saves at least 15 minutes of operating time.

IV. PARATHYROIDECTOMY

SURGICAL COURSE OF CASE PATIENT 1

A bilateral neck exploration is performed on patient 1. At surgery, he is noted to have a 2.5 × 2.0 × 1.0-cm right inferior parathyroid adenoma located retrosternally within a cervical tongue of atrophic thymus (Figure 4). The gland, which is subsequently removed, weighs 2.55 g. Three other parathyroid glands are identified and are normal in appearance. Patient 1’s postoperative course is unremarkable. The morning after surgery, he is discharged with a serum calcium level of 9.2 mg/dL.

- What is involved in the surgical treatment of hyperparathyroidism?
DISCUSSION

Treatment Approaches

Currently, parathyroidectomy is the only definitive treatment for primary hyperparathyroidism. All patients with signs, symptoms, or metabolic complications associated with the disorder should undergo neck exploration and resection of abnormal parathyroid tissue. The management of asymptomatic disease continues to be controversial because of the somewhat unpredictable clinical course of primary hyperparathyroidism. Patients may remain asymptomatic from many years without developing metabolic complications. In general, outcomes data are not available for patients with apparent asymptomatic disease who are not surgically treated. In 1991, a list of indications for parathyroid surgery was published based on the National Institutes of Health (NIH) Consensus Development Conference on the diagnosis and management of asymptomatic hyperparathyroidism (Table 3).2 Since then, it has become evident that primary hyperparathyroidism (both symptomatic and asymptomatic) is associated with increased mortality.3–12 Surgical treatment has also been shown to reduce or eliminate the risk of premature death.12 Thus, all patients with primary hyperparathyroidism (except the elderly, asymptomatic, high-risk patient) should undergo parathyroidectomy at an early stage.11,12

Treatment of primary hyperparathyroidism depends on parathyroid pathology. For patients with a single or double adenoma, excision of the adenoma is adequate treatment. A frozen-section examination of excised tissue is performed to confirm the presence of parathyroid tissue. There is no need for routine biopsy of normal parathyroid glands.

In patients with 4-gland hyperplasia, a subtotal parathyroidectomy and bilateral transcervical thymectomy should be performed.17,27 This is accomplished by first performing a subtotal resection of 1 parathyroid gland and leaving a remnant that approximates the weight of a normal gland (35 to 50 mg). Once a viable remnant has been established, the other 3 parathyroid glands are removed in their entirety. Transcervical thymectomy is performed because in patients with parathyroid hyperplasia, there is a 10% to 15% incidence of supernumerary parathyroid glands, which are most often located within the thymus.27

An alternative treatment for parathyroid hyperplasia is total parathyroidectomy, transcervical thymectomy, parathyroid autotransplantation into the brachioradialis muscle of the nondominant forearm, and parathyroid cryopreservation.28 Although the incidence of persistent or recurrent hyperparathyroidism is similar after total or subtotal parathyroidectomy,29 total parathyroidectomy carries a higher incidence of permanent hypoparathyroidism. Late failure of parathyroid autografts have been reported in 25% of patients with secondary hyperparathyroidism who have undergone total parathyroidectomy and autotransplantation.30 Because of this, subtotal parathyroidectomy is the preferred treatment for parathyroid hyperplasia.

Patients with parathyroid carcinoma are treated with an en bloc resection of the parathyroid tumor and tissues invaded by the tumor, most commonly the thyroid gland and the strap muscles. A modified neck dissection should be performed for associated lymph node metastases. The tumor capsule should not be violated during resection because tumor spillage may lead to

Table 3. Indications for Parathyroid Surgery

| Patients with serum calcium levels greater than 11.5–12.0 mg/dL |
|Patients whose creatinine clearance is reduced more than 30% for age in the absence of another cause |
|Patients whose 24-hour urinary calcium is greater than 400 mg/dL |
|Patients whose bone mineral density is reduced more than 2 standard deviations compared with age-matched, gender-matched, and race-matched controls |
|Patients who request surgery or in whom long-term surveillance is unsuitable |
|Patients younger than 50 years |

NIH = National Institutes of Health.


Figure 4. Excised thymic tissue with a large intrathymic parathyroid adenoma (2.5 × 2.0 × 1.0 cm). This adenoma corresponded to the radioactivity focus in the right retrosternal position, noted on preoperative scan (see Figure 1).
recurrent hypercalcemia secondary to multiple tumor implants in the soft tissue, a condition known as parathyromatosis.

Although several surgical approaches are advocated for the definitive treatment of primary hyperparathyroidism, the gold standard remains bilateral neck exploration with examination of the 4 parathyroid glands. By examining all 4 glands, the presence or absence of multiglandular disease can be established, reducing the likelihood of persistent hyperparathyroidism from double adenoma or unrecognized asymmetric hyperplasia.

Another approach to the patient with primary hyperparathyroidism consists of routine preoperative parathyroid localization with Tc-99m-sestamibi scintigraphy, a unilateral neck exploration when a solitary adenoma is demonstrated, and an intraoperative “quick” PTH assay (which has a turn-around time of approximately 10 to 15 minutes) to confirm the removal of all pathologic parathyroid tissue. PTH has a half-life of 3 to 5 minutes; a 50% reduction in PTH measured 10 minutes after removal of an adenoma is predictive of a curative resection. The advantage to this approach is that exploration can be limited to one side of the neck. Disadvantages include the expense of the “quick” assay and the fact that in the 20 to 30 minutes from the time of adenoma resection until PTH results become available, the opposite side of the neck could have been explored. Use of the intraoperative PTH assay may be valuable for operations performed for persistent or recurrent hyperparathyroidism.

RADIOGUIDED AND VIDEOSCOPIC PARATHYROIDECTOMY

A new technique for treating hyperparathyroidism is radioguided parathyroidectomy. In this procedure, patients undergo a preoperative Tc-99m-sestamibi scan, and those who are diagnosed with a solitary parathyroid adenoma are injected with sestamibi on the day of surgery. Patients are operated on 1.5 to 2.5 hours after sestamibi injection. A hand-held gamma detection device with a parathyroid probe is used to locate the adenoma and to direct dissection. The increased radioactivity within the adenoma is confirmed ex vivo, eliminating the need for frozen-section examination. After removal of an adenoma, equalization of radioactivity throughout the neck is indicative of a curative resection and eliminates the need for further dissection. Radioguided parathyroidectomy is being used as initial treatment for primary hyperparathyroidism and as treatment for persistent or recurrent disease.

Most recently, videoscopic parathyroidectomy has been advocated in the management of hyperparathyroidism because of the procedure’s potential cosmetic advantages. Videoscopic parathyroidectomy is performed as described by Miccoli. A 15-mm horizontal skin incision is made at the level of the sternal notch, and a 12-mm trocar is inserted between the strap muscles and thyroid gland. Carbon dioxide insufflation is completed, and the trocar is removed. The operative space is maintained with small external retractors. The parathyroidectomy is performed by using a 30-degree, 5-mm endoscope and 2-mm needlescopic instruments that are placed through the skin incision. Vascular clips are used for ligation of the blood supply to the abnormal parathyroid gland. If necessary, additional ports can be placed laterally in the neck. At present, this approach is technically challenging, expensive, and has the same potential drawbacks of any limited neck exploration. Further studies are needed before the role of videoscopic parathyroidectomy can be determined in the treatment of primary hyperparathyroidism.

URGENT PARATHYROIDECTOMY

Urgent parathyroidectomy is necessary in patients with hypercalcemic crisis. In these cases, parathyroidectomy is performed after initial treatment of acute hypercalcemia and its manifestations. Any agents known to cause hypercalcemia, such as thiazide diuretics or lithium, are discontinued. Volume deficit is corrected with an infusion of normal saline solution, which expands the extracellular fluid volume and increases urinary calcium excretion. A Foley catheter is placed to ensure adequate urinary output. As soon as dehydration has been corrected and the patient is euvoletic, a potent diuretic such as furosemide may be given to increase calcium excretion. For further reduction in serum calcium levels, a single 60- to 90-mg dose of intravenous pamidronate can be administered. Pamidronate is a bisphosphonate, a class of drugs that produces a profound decrease in serum calcium by osteoclast inhibition. However, normalization of calcium occurs gradually during 3 to 6 days. Calcitonin, which also acts by inhibiting osteoclast activity, may be used to produce a more rapid decline in serum calcium, usually within hours of administration. The therapeutic effect of calcitonin is short-lived; therefore, a 4 U/kg dose is usually given every 12 hours.

V. RESULTS OF SURGICAL THERAPY

When performed by an experienced surgeon, parathyroidectomy leads to a cure of primary hyperparathyroidism in 95% to 99% of patients, with an incidence of recurrent laryngeal nerve injury and permanent hypoparathyroidism of less than 1%. Commonly,
patients may develop temporary postoperative hypocalcemia secondary to “bone hunger,” a condition in which bone retrieves calcium that was depleted when serum PTH levels were high. This condition usually presents with acral or perioral numbness or paresthesias and occasional muscle cramps. Rarely, patients may develop tetany manifested by trismus or carpopedal spasm. Chvostek’s sign (twitching of the ipsilateral upper lip elicited by tapping the facial nerve just below the zygoma) or Trousseau’s sign (flexion of the metacarpophalangeal joints and extension of the interphalangeal joints elicited by inflating a blood pressure cuff just above systolic pressure and maintaining it for 3 minutes) may be evident on physical examination. Postoperative hypocalcemia can be treated on an outpatient basis with 500 to 1000 mg elemental calcium carbonate 2 to 4 times daily. If symptoms persist despite calcium therapy, 0.25 to 0.50 µg of 1,25-dihydroxyvitamin D₃ twice daily may be started. In most patients, temporary postoperative hypocalcemia resolves within 2 weeks of surgery.

RISK AND SYMPTOM REDUCTION AFTER PARATHYROIDECTOMY

The risk of premature death that has been reported in asymptomatic and symptomatic patients with hyperparathyroidism is reduced by surgery, especially when performed early and in young patients. The death rate returns to normal, 5 to 15 years after surgical intervention. After parathyroidectomy, patients experience complete resolution of the bony abnormalities of osteitis fibrosa cystica. The decreased concentrating ability of the renal tubules also resolves completely after parathyroidectomy. Stone formation is halted in 90% of patients with nephrolithiasis. Regression of left ventricular hypertrophy has also been reported after surgical treatment of hyperparathyroidism. Nonspecific symptoms (including fatigue, malaise, and muscle weakness) disappear in 80% of patients, and psychiatric symptoms often improve. Surgical correction of primary hyperparathyroidism significantly improves patients’ reported functional health status and overall quality of life.

In general, hypertension and impaired renal function do not improve after surgery for primary hyperparathyroidism, although the progression of both is halted. In addition, parathyroidectomy may partially reverse loss of bone mineral density, although in most patients it improves only to about 75% of normal. The irreversibility of certain metabolic conditions should be recognized, and delays in recommending definitive parathyroidectomy for patients with primary hyperparathyroidism should be avoided.

VI. SUMMARY POINTS

- Untreated hyperparathyroidism is associated with premature death as a result of cardiovascular disease and, less commonly, as a result of malignancy and renal failure.
- In a patient with hypercalcemia, a diagnosis of hyperparathyroidism is made by documenting an elevated intact serum PTH level using an immunoradiometric or chemiluminescence assay.
- The imaging study with the greatest sensitivity for localizing abnormal parathyroid tissue is technetium-99m-scintigraphy.
- Parathyroidectomy is the only definitive treatment for primary hyperparathyroidism.

BOARD REVIEW QUESTIONS

Choose the single best answer for each question.

1. Which of the following localizing studies has the highest overall sensitivity for detecting a parathyroid adenoma?
   A) Ultrasound
   B) Technetium-99m-sestamibi scintigraphy
   C) Computed tomography (CT)
   D) Magnetic resonance imaging (MRI)

2. A 60-year-old woman is admitted with nausea, vomiting, confusion, a calcium level of 16 mg/dL, and a PTH level of 458 pg/mL. The initial therapeutic intervention should consist of:
   A) Intravenous (IV) furosemide
   B) IV pamidronate
   C) IV normal saline
   D) Immediate parathyroidectomy

3. What is the most frequent metabolic complication of primary hyperparathyroidism?
   A) Osteitis fibrosa cystica
   B) Nephrolithiasis
   C) Gout
   D) Peptic ulcer disease
   E) Pancreatitis

4. What pathology is most likely to be seen in a patient with familial hyperparathyroidism?
   A) A single adenoma
   B) A double adenoma
   C) Hyperplasia of all 4 parathyroid glands
   D) Parathyroid carcinoma
5. **What does surgical treatment of hyperparathyroidism resolve?**
   A) Hypertension
   B) Impaired renal function
   C) Reduced bone mineral density
   D) Osteitis fibrosa cystica

**DETAILED ANSWERS**

1. (B) Technetium-99m-sestamibi scintigraphy. Ultrasound, CT, and MRI all have a sensitivity of approximately 60% to 70%. The sensitivity of technetium-99m-sestamibi scintigraphy, however, has been reported to be 80% to 90%. Because of this increased sensitivity, imaging with technetium-99m-sestamibi scintigraphy should be the initial procedure for parathyroid localization.

2. (C) IV normal saline. The initial therapeutic intervention in this patient with hypercalcemic crisis should consist of administration of IV normal saline to rapidly expand the extracellular fluid volume and to increase urinary calcium excretion. IV furosemide is a potent diuretic that may also increase calcium secretion, but furosemide should not be administered until dehydration has been corrected. Once volume depletion has been corrected, further reduction in serum calcium levels may be produced by administration of pamidronate; however, it works gradually to normalize calcium levels over 3 to 6 days. Immediate parathyroidectomy would be dangerous before correcting the extracellular fluid volume deficit that exists in patients in hypercalcemic crisis.

3. (B) Nephrolithiasis. Most patients with primary hyperparathyroidism present with apparent asymptomatic disease, although if questioned they usually report nonspecific symptoms such as fatigue, malaise, muscle weakness, constipation, or depression. Nephrolithiasis is the most frequent metabolic complication of hyperparathyroidism, occurring in 15% to 20% of patients. Osteitis fibrosa cystica, gout, peptic ulcer disease, and pancreatitis are rare.

4. (C) Hyperplasia of all 4 parathyroid glands. Hyperplasia of all 4 glands is the parathyroid pathology in 80% or more of patients with familial hyperparathyroidism and in only 15% of patients with sporadic hyperparathyroidism. In sporadic hyperparathyroidism, single adenomas occur in 80% or more of patients. Double adenoma and carcinoma account for 4% and 1% of all cases of sporadic primary hyperparathyroidism, respectively.

5. (D) Osteitis fibrosa cystica. Skeletal abnormalities associated with osteitis fibrosa cystica resolve completely after parathyroidectomy. The reduced bone mineral density that occurs as a result of hyperparathyroidism improves to approximately 75% of normal. Secondary hypertension and impaired renal function are irreversible, although the progression of both is halted by parathyroidectomy.

**REFERENCES**


