Chapter 35
Parathyroid Disease in the Elderly

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CASE STUDY

An 82-year-old woman was brought to the Emergency Department with a 5-day history of worsening lethargy and confusion. From prior hospital records, her past medical history was notable for two episodes of nephrolithiasis, gastroesophageal reflux disease, and hypertension. Her medications included hydrochlorothiazide, metoprolol, omeprazole, and aspirin.

Physical examination revealed a frail-appearing woman, who was arousable to voice, and oriented only to person. She was afebrile and normotensive, but mildly tachycardic with a heart rate of 100 beats per minute. Neurologic exam was nonfocal. The remainder of her examination was significant only for poor skin turgor and dry mucous membranes.

Laboratory studies were notable for a normal white blood cell count, mild hemoconcentration, blood urea nitrogen (BUN) 25 mg/dL, serum creatinine 1.3 mg/dL, serum calcium 14.7 mg/dL, and albumin 4.3 g/dL. Urinalysis was negative.

The patient was admitted to the hospital with hypercalcemia. She was hydrated appropriately with intravenous crystalloid fluids, with subsequent improvement of her mental status and calcium level. Additional laboratory evaluation was obtained, revealing an intact parathyroid hormone (iPTH) level of 200 pg/ml. The patient was diagnosed with primary hyperparathyroidism.

Introduction

The primary function of the parathyroid glands is to maintain calcium homeostasis through the secretion of parathyroid hormone (PTH). This hormone is regulated by serum calcium through calcium-sensing receptors (CaSRs) on the parathyroid cell surface. In turn, most peripheral tissues, primarily kidney and bone, have PTH receptors which can affect varying functions. In the past, disturbances in this system were difficult to recognize until the development of clinically significant disease. With the development of better biochemical assays for serum PTH and calcium levels, subclinical derangements can be diagnosed before patients become symptomatic. The management of patients with the broad spectrum of metabolic calcium disturbances remains controversial.

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Mineral Homeostasis

Plasma calcium exists in three phases: protein-bound, ionized, and complexed. Normally, approximately 1 g of inorganic calcium is absorbed daily in the proximal small intestine. About 45% of total blood calcium is protein-bound, predominantly to albumin, but also to globulins. A similar fraction is ionized. The rest is complexed to organic ions such as citrate, phosphate, and bicarbonate. Calcium is in constant flux between the extracellular and intracellular spaces, in bone, and in renal glomerular filtrate, which is reabsorbed by the normal kidney.

The ionized fraction of serum calcium controls vital cellular functions, such as neuromuscular transmission, muscle contraction, and blood clotting. Precise maintenance of calcium concentration within a very narrow range in extracelluar fluids is therefore critically important. The binding of calcium to albumin is pH-dependent, increasing with alkalosis, and decreasing with acidosis. Thus, if the ionized calcium is low, acidosis tends to protect an individual from manifesting the symptoms and signs of hypocalcemia; conversely, alkalosis predisposes a patient to symptomatic hypocalcemia.

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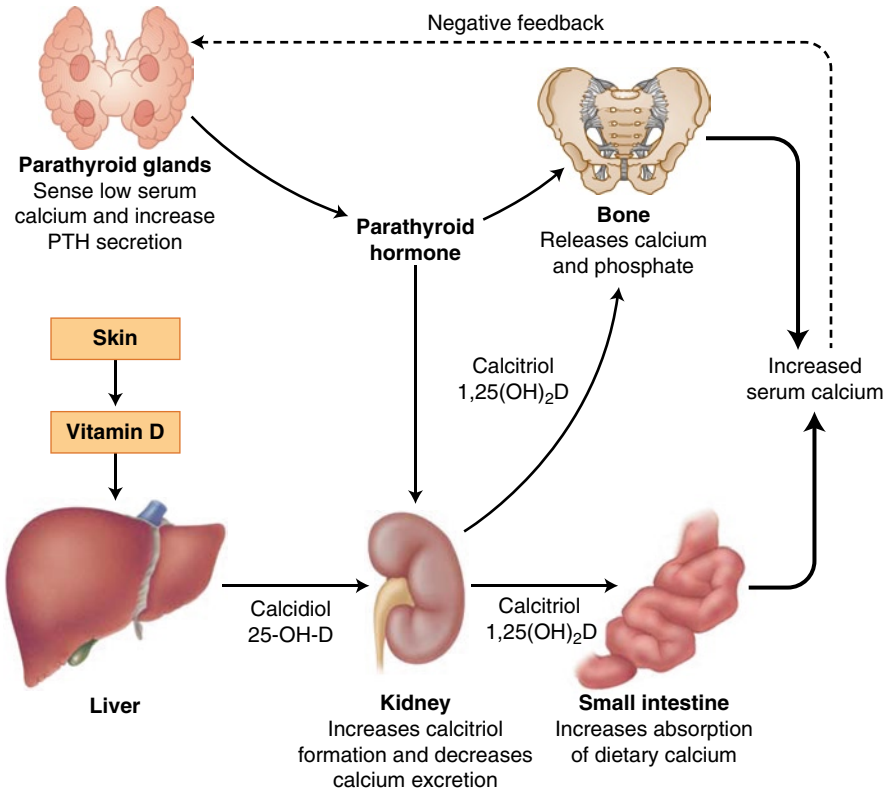

Figure 35.1 Calcium metabolism.

The adult body contains approximately 700 g of phosphate, primarily located in the teeth and bones. Plasma levels of calcium and phosphate are inversely related, and the primary agents responsible for calcium metabolism are PTH, vitamin D, and calcitonin (see Fig. 35.1) [1].

Parathyroid Hormone (PTH)

The chief cells of the parathyroid gland constantly monitor ionized calcium concentrations through their cell surface CaSR, thus allowing the circulating level of PTH to change within seconds after an alteration in serum calcium [2]. PTH secretory rates are related to serum ionized calcium and 1,25-dihydroxyvitamin D by an inverse sigmoidal relationship. Low ionized calcium concentrations maximally stimulate secretion, while increases in calcium suppress the production and release of PTH. PTH secretion is exquisitely sensitive to very small alterations in the calcium concentration, which have substantial effects on the rate of hormone synthesis and release.

PTH is synthesized within the parathyroid gland as a 115-amino-acid precursor molecule (preproPTH) that is successively cleaved within the cell to form the mature 84-amino-acid PTH. This form of the hormone is packaged into secretory granules and released into the circulation. Mature PTH is metabolized in the liver into the active N-terminal and inactive C-terminal fragments. The intact molecules and N-terminal fragments have half-lives of approximately 3–5 min, while the inactive C-terminal fragments have a half-life of hours. The C-terminal fragments are excreted by the kidneys, and usually accumulate to high levels in the serum of patients with renal failure.

PTH inhibits osteoblasts and stimulates osteoclasts. In the kidney, PTH causes a decrease in calcium clearance as well as increased renal excretion of phosphate by inhibiting its reabsorption in the tubules. In addition, PTH stimulates hydroxylation of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, which allows for enhanced calcium absorption in the proximal intestine [3].

Vitamin D

The sterol 1,25-dihydroxyvitamin D, or calcitriol, is an essential mediator of calcium homeostasis. Calcitriol synthesis begins with ultraviolet activation of 7-dehydrocholesterol in the skin, generating cholecalciferol (vitamin D). In the liver, vitamin D is readily hydroxylated to 25-hydroxyvitamin D2,

which in turn is hydroxylated to the potent calcitriol. This final step occurs in the kidney and is tightly regulated by PTH. In turn, calcitriol has a regulatory effect on PTH, by exerting a physiologic inhibition of the parathyroid glands [4].

Calcitonin

Parafollicular, or C cells, of the thyroid gland secrete the peptide hormone calcitonin. Calcitonin interacts with receptors in kidney and bone. The primary function of calcitonin is to lower serum calcium, and this hormone is released rapidly in response to hypercalcemia. It inhibits osteoclastic bone resorption and quickly blocks the release of calcium and phosphate from bone. Ultimately, this effect, along with the inhibition of resorption, leads to a fall in serum calcium and phosphate [3]. The physiologic effect of calcitonin in humans, however, is very modest.

Hypercalcemia

The most common reason for the finding of hypercalcemia in an elderly patient, in the oupatient setting, is primary hyperparathyroidism (HPTH), while hypercalcemia in the inpatient population often is secondary to malignancies. Diagnosing the correct etiology requires careful clinical evaluation of patients, as well as serologic and biochemical testing (Table 35.1) [5].

After a thorough history and physical examination, laboratory measurements of fasting serum calcium, PTH, creatinine, and vitamin D levels should be performed to determine if the hypercalcemia is parathyroid-mediated (in which serum PTH levels are elevated inappropriately) or non-parathyroid-mediated (in which serum PTH levels are suppressed appropriately). Normally, functioning parathyroid cells abruptly cease PTH release when the surrounding extracellular fluid calcium concentration is elevated. Therefore, in cases in which hypercalcemia results from a non-parathyroid-mediated condition, serum PTH levels will be suppressed [6].

Table 35.1 Differential diagnosis of hypercalcemia

Parathyroid-mediated	Non-parathyroid-mediated
Primary hyperparathyroidism	Malignancy-associated hypercalcemia
Parathyroid adenoma (85%)	Local osteolytic hypercalcemia
Parathyroid hyperplasia (15%)	Humoral hypercalcemia of malignancy (PTHrP and calcitriol)
Parathyroid carcinoma (<1%)	Granulomatous disease (sarcoidosis and tuberculosis)
Secondary/tertiary hyperparathyroidism	Endocrinopathies (hyperthyroidism and adrenal insufficiency)
Familial hypocalciuric hypocalemia	Drugs (thiazides, vitamin D and calcium)
Lithium therapy	Immobilization

Source: Modified and reproduced from [1]

Non-Parathyroid-Mediated Hypercalcemia

This category includes conditions in which patients have hypercalcemia and serum PTH levels that are suppressed appropriately; the parathyroid cells perceive excess extracellular calcium concentrations, and markedly reduce their hormonal release. Cancer is the most frequently diagnosed etiology of non-PTH-mediated hypercalcemia, particularly in the hospitalized population. This malignancy-associated hypercalcemia is classified into two primary forms, osteolytic and humoral.

The second form of malignancy-associated hypercalcemia is local osteolytic hypercalcemia, which occurs when a neoplasm directly invades the bony skeleton, resulting in localized destruction and calcium release. In contrast to malignant humoral hypercalcemia, local osteolytic hypercalcemia does not involve the elaboration of systemically active products. Rather, it appears to result from the production or local stimulation of bone-active cytokines as well as other osteoclast-activating factors. This form of pathologic hypercalcemia is most commonly associated with multiple myeloma; however, it has also been linked to adenocarcinoma of the breast and certain lymphomas [7].

Humoral hypercalcemia of malignancy results from the systemic effect of a circulating factor produced by the neoplasm. Most commonly, the factor involved is parathyroid hormone-related protein (PTHrP), a peptide that has been shown to recapitulate most of the metabolic effects of PTH, including stimulation of bone turnover and alteration in renal handling of both calcium and phosphate [7]. In humans, PTHrP serves as an important paracrine factor in may tissues, including skin, bone, breast, the central nervous system, and the vasculature. Neoplasms that elaborate PTHrP include squamous cell carcinomas (naso- and oro-pharynx, larynx, lung, esophagus, and cervix), adenocarcinoma of the breast and ovary, bladder transitional cell carcinoma, T-cell lymphomas, renal cell carcinoma, and carcinoid tumors. The other factor that may cause malignant humoral hypercalcemia is calcitriol, which is often associated with B-cell lymphomas [7, 8].

There are other benign, non-PTH-mediated causes of hypercalcemia encountered in the elderly. These include medications and supplements, such as thiazide diuretics and excess exogenous calcium, vitamin D, or vitamin A. Granulomatous diseases, such as sarcoidosis and tuberculosis, are associated with hypercalcemia through the direct production of calcitriol. In addition, several endocrinopathies are associated with hypercalcemia, including hyperthyroidism with augmented bone turnover, pheochromocytoma with PTHrP production, and adrenal insufficiency linked with decreased calcium clearance. Rarely, hypercalcemia may result from prolonged immobilization, particularly in settings in which bone turnover is already stimulated, such as recovery from fractures or surgery [3].

Parathyroid-Mediated Hypercalcemia

The differential diagnosis of parathyroid-mediated hypercalcemia includes HPTH, familial hypocalciuric hypocalcemia (FHH), and lithium therapy. The remainder of this chapter will focus primarily on the forms and treatment strategies of HPTH. However, FHH and lithium therapy briefly are discussed below, as the differences between these diagnoses are important.

FHH, also known as benign familial hypercalcemia, is an inherited autosomal dominant condition resulting from a deactivating mutation in the extracellular CaSR [9]. In this condition, the cell surface receptor is sub-normally activated by extracellular calcium. In the face of mild elevation of serum calcium, PTH levels are inappropriately normal or slightly elevated. However, urinary calcium excretion is reduced, due to the same defective CaSRs in the nephron, with subsequent increased urinary calcium reabsorption. Although FHH is classified as parathyroid-mediated, since PTH secretion is abnormal, it is a unique condition and distinct from the more common primary HPTH. Generally, it is diagnosed in younger patients with asymptomatic, mild hypercalcemia. The family history usually identifies affected relatives. It does not require surgical intervention, as parathyroidectomy will not cure the condition.

Chronic lithium therapy may increase serum calcium levels with inappropriately normal or mildly elevated PTH concentrations. Lithium appears to alter the sensitivity of the CaSR, thus increasing the set-point of extracellular calcium concentration. However, parathyroid adenomas and multigland hyperplasia have also been described in patients chronically treated with lithium [10]. Distinguishing those patients with drug-induced hypercalcemia from those with mild primary HPTH can be challenging.

Hyperparathyroidism

Hyperparathyroidism was first recognized during the 1920s and was thought to be a relatively uncommon condition, presenting usually as nephrolithiasis or as a complication of severe bony demineralization [5]. With the application of multiphasic blood testing revealing elevated serum calcium concentrations and the availability of accurate PTH determinations, HPTH now is recognized to be a more common disorder, particularly in the elderly population.

Primary Hyperparathyroidism

Primary hyperparathyroidism is the most common form of HPTH and is the most frequent explanation for hypercalcemia in the outpatient setting. Population-based estimates reveal an overall incidence of approximately 25 per 100,000 in the general population with about 50,000 new cases occurring annually. The peak incidence is in the fifth to sixth decade of life, with a female to male ratio of about 3:2. Some studies estimate the overall prevalence of HPTH in the elderly at 2–3%, with approximately 200 cases/100,000 population [11].

The most common clinical presentation is that of asymptomatic, or minimally symptomatic, mild hypercalcemia. Primary HPTH generally is caused by a benign, solitary parathyroid adenoma in 80–85% of patients. In about 5% of patients, two distinct adenomas ("double adenoma") are found. Multigland parathyroid hyperplasia is present in 15–20%. In younger patients, this may be associated with familial syndromes, such as multiple endocrine neoplasia (MEN) types I and IIA. Patients with MEN-I have enlargement and hyperfunction of all parathyroid glands, whereas patients with MEN-IIA may have asymmetric parathyroid gland enlargement. The rare hyperparathyroidism-jaw tumor syndrome is another autosomal dominant inherited condition presenting with early-onset primary HPTH and fibro-osseous, cystic jaw neoplasms [12, 13]. Index cases of MEN syndromes are rare in the elderly patients, but certain mutations may manifest later in life, therefore in the appropriate clinical setting, MEN needs to be considered even in elderly patients.

Parathyroid carcinoma is a rare cause of primary HPTH, accounting for less than 1% of cases. In contrast to benign HPTH, it occurs equally in men and women. Patients with parathyroid carcinoma present most often in the fifth and sixth decades of life. Longstanding untreated primary HPTH may devolve into parathyroid carcinoma, which may then present in the elderly patients [14]. Although these tumors are slow-growing, they have a high propensity to recur locally, and recurrent disease is difficult to eradicate. Patients with recurrent and metastatic disease often suffer from severe, debilitating hypercalcemia, control of which may involve palliative surgical resection and the use of drugs, including bisphosphonates and calcimimetics, to lower the serum calcium level [15, 16].

Clinical and Diagnostic Evaluation

With the advent of routine serum calcium screening, the typical presentation of primary HPTH has changed from a severe, debilitating illness to a disease with subtle symptoms and physiologic derangements. Common signs include nephrolithiasis, nephrocalcinosis, osteopenia, and osteoporosis (Table 35.2) [17]. Hypertension is frequently present in patients with primary HPTH, and a variety of mechanisms have been proposed to explain this relationship. It appears to be most closely correlated with the degree of renal impairment seen in patients with hypercalcemia. However, one

Table 35.2 Symptoms and associated conditions in patients with primary hyperparathyroidism

Symptoms
Weakness, exhaustion, and fatigue
Bone pain, back pain, and joint pain
Polyuria, nocturia, and polydipsia
Loss of appetite, nausea, and dyspepsia
Memory loss and depression
Associated conditions
Weight loss
Bone fracture, joint swelling, and gout
Nephrolithiasis, hematuria from passage of renal calculus
Gastric ulcer, duodenal ulcer, and pancreatitis
Hypertension

study found that parathyroidectomy led to a substantial fall in both systolic and diastolic pressures in 54% of hypertensive subjects that appeared to be unrelated to improvement in renal function [18]. Most endocrine specialists do not believe that curative surgery in primary HPTH is associated with a significant improvement in hypertension.

There are many subtle abnormalities associated with primary HPTH, including decreased cognitive function, depression, lethargy, myalgias, arthralgias, constipation, and urinary symptoms, such as increased thirst and urinary frequency. Petersen performed psychiatric examinations on 54 patients with primary HPT and detected mental disturbances in more than 50% [19, 20]. However, it is often difficult to prove that these nonspecific findings result from primary HPTH because they are common in the elderly. In a general population cohort study of over 4,000 individuals, Schram et al. found that serum calcium levels that were at the upper range of normal or frankly elevated were associated with faster decline in cognitive function, particularly for patients over the age of 75 years [21].

The diagnosis of primary HPT typically is made by biochemical evidence of an elevated serum calcium concentration, usually in conjunction with an elevated serum intact PTH. Approximately half of patients with primary HPTH have hypophosphatemia. However, in the presence of significant renal impairment, serum phosphate levels may be elevated. Because of the effect of PTH on bicarbonate excretion in the kidney, patients with primary HPTH often have a hyperchloremic metabolic acidosis [13]. Approximately 10–40% of HPTH patients have elevated levels of alkaline phosphatase, which indicates some degree of increased bone turnover. Although osteitis fibrosa cystica, the classic form of parathyroid bone disease, is rarely seen today, even patients with mild disease can be seen to have biochemical or histologic evidence of bone involvement. Dual-energy X-ray absorption (DEXA) scanning of the lumbar spine, hip, and forearm has become the standard method for assessing bone density to diagnose osteoporosis in the setting of primary HPTH [22–24].

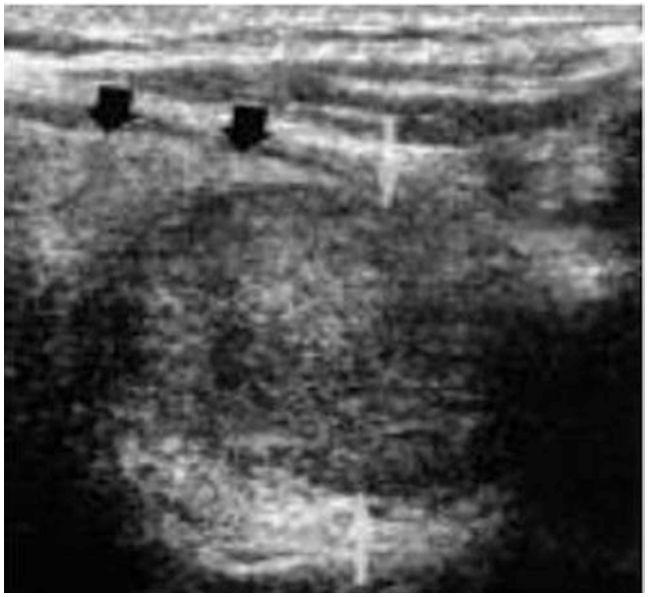

Figure 35.2 Parathyroid adenoma. Sagittal ultrasound shows a parathyroid adenoma (*white arrows*) behind the lower pole of the right thyroid lobe (*black arrows*).

Patients with FHH must be distinguished from those with primary HPTH. This can be done with a 24-h urinary calcium excretion study, which is uniformly low in the setting of FHH. In contrast, patients with primary HPTH have a normal or elevated 24-h urinary excretion of calcium [9]. Postmenopausal women often have hypercalciuria for several years after the onset of menopause from estrogen decrease, therefore increased urinary calcium levels in this population may not always be due to hyperparathyroidism.

Although rare, parathyroid carcinoma should be suspected in patients who demonstrate a rapid and sustained rise in both their serum calcium and PTH levels. A palpable neck mass sometimes may be appreciated [25, 26]. A parathyroid adenoma is rarely, if ever, palpable on physical examination. Rather, this neck mass is more likely to represent a thyroid nodule.

There have been extensive discussions regarding the use and availability of preoperative imaging studies in patients with primary HPT. In the past, patients who had not undergone previous surgical exploration did not require any radiographic localization studies other than finding an experienced parathyroid surgeon. However, the increased use of minimally invasive parathyroidectomy techniques has mandated preoperative imaging.

Imaging studies can be sorted into noninvasive and invasive techniques. The noninvasive studies include the following: nuclear medicine scans, such as methoxyisobutylisonitrile (sestamibi) studies, which can be combined with single photon emission computed tomography (SPECT) imaging; ultrasound (Fig. 35.2); computed tomography (CT) scans; and magnetic resonance imaging (MRI). The noninvasive

localization study of choice is a technetium (^{99m}Tc)-sestamibi scan with SPECT, which results in a three-dimensional reconstruction that can delineate the location of an enlarged parathyroid gland in 85% of cases (Fig. 35.3a, b).

Invasive techniques usually are reserved for re-operative cases, and include angiography and venous sampling for PTH gradients. Recently, the rapid PTH assay has been used in both the angiography suite as well as the operating room. It yields real-time feedback and has become invaluable in the development of minimally invasive techniques [27–29].

Most patients presenting with primary HPT are asymptomatic, or mildly, chronically ill with vague symptoms referable to the kidneys or the musculoskeleton. However, patients may become acutely and severely ill with acute hypercalcemia, or hyperparathyroid crisis. This disorder often can be seen in elderly patients, nursing home residents, or patients with cognitive deficits, such as dementia. Such patients often harbor mild to moderate hyperparathyroidism for years, but an inciting factor will cause acute worsening of the hypercalcemia. The most common etiology is simple dehydration from poor health, overuse of diuretic medications, gastroenteritis or viral illness. The onset is usually characterized by rapidly developing muscular weakness, nausea and vomiting, weight loss, drowsiness, fatigue, and confusion. The serum calcium concentration almost always is remarkably elevated (16–20 mg/dL). The offending parathyroid gland is usually large. The genesis of the condition involves uncontrolled PTH secretion followed by hypercalcemia, polyuria, dehydration, and reduced renal function, which worsens the hypercalcemia [10].

The management of severe hypercalcemia incorporates four primary aims: to correct dehydration; to enhance renal excretion of calcium; to inhibit bone resorption; and to treat the underlying disorder. Although the definitive therapy is resection of the hyperfunctioning parathyroid gland, it is unsafe to proceed with operative exploration until the serum calcium concentration is lowered. Resuscitation with 0.9% normal saline is instituted to maintain urinary output above 100 ml/h, and subsequent diuresis with loop diuretics increases the renal excretion of sodium and calcium. In the elderly patients, care must be taken to assess their cardiac function, so as to avoid overhydration and fluid overload. If the serum calcium level remains elevated, other agents that can lower the serum calcium concentration should be administered. These agents include bisphosphonates, calcitonin, and cinacalcet [10]. Often, multidisciplinary care is needed for these complex patients.

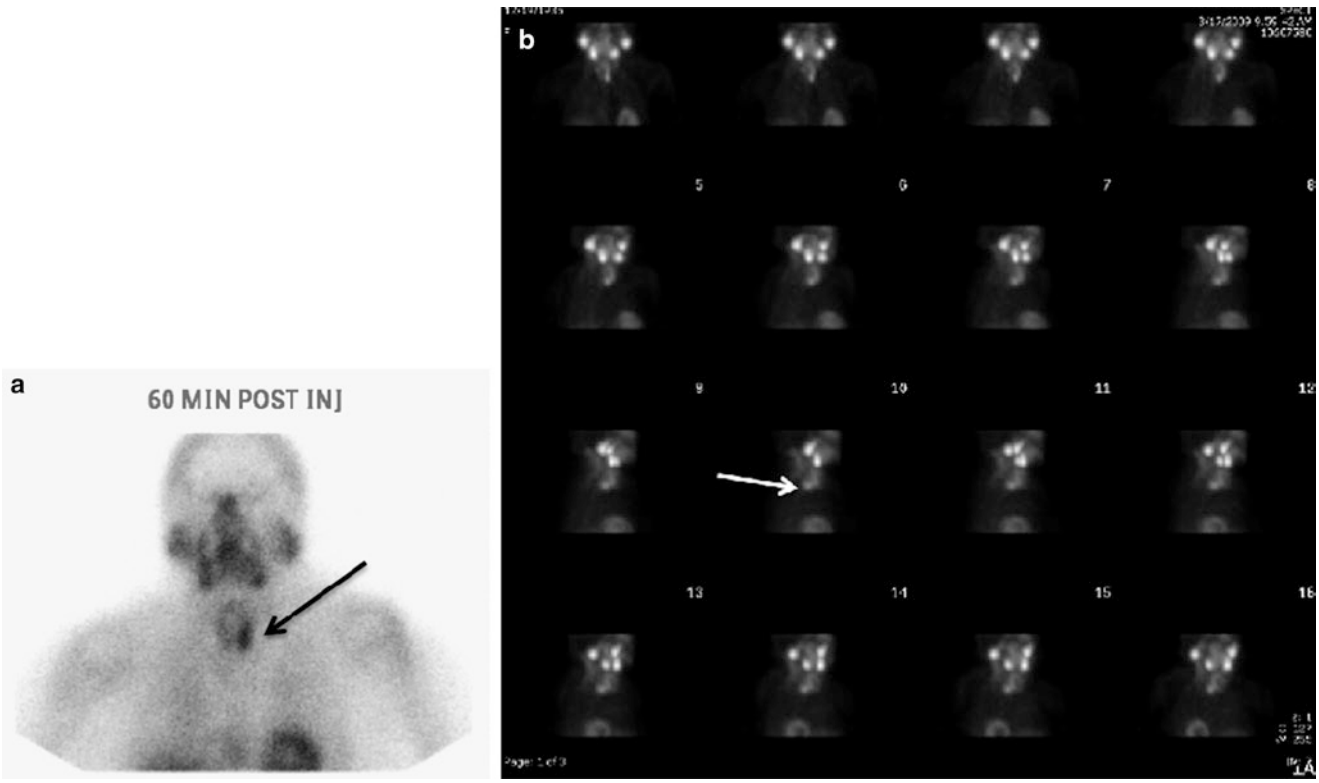

Figure 35.3 (**a**) Scintigraphic image from ^{99m}Tc-sestamibi depicting a left-sided parathyroid adenoma (*arrow*) in primary hyperparathyroidism (**b**) Scintigraphic images from sestamibi single-photon-emission tomography of the same patient presented in (**a**) depicting multiple rotational tomographic planes. The posterior location of the parathyroid adenoma (*arrow*) is consistent with a superior parathyroid gland.

Treatment

There has been considerable debate regarding the management of elderly patients with primary hyperparathyroidism. There is universal agreement that patients with clear symptoms and signs associated with hyperparathyroidism should undergo parathyroid surgery because parathyroidectomy is the only long-term effective treatment. However, controversy still exists about the management of patients with "asymptomatic" primary HPTH [30, 31]. Recent data suggest that these asymptomatic patients often have symptoms that are recognized in retrospect, once their HPTH has been cured. In addition, asymptomatic patients may suffer from neurocognitive deficits, depression, and anxiety, as well as progressive cardiovascular disease, and a suggestion of insulin resistance, which can result in premature death [32, 33].

In 1990 and 2002, the National Institutes of Health (NIH) convened consensus conferences to delineate the surgical indications in patients with both symptomatic and asymptomatic primary HPTH (Table 35.3) [34, 35]. In 2008, an international workshop on HPTH convened to review and update previous recommendations [36]. Guidelines also were created for the management of patients with asymptomatic primary HPTH who did not undergo surgery, including biannual serum calcium and annual serum creatinine measurements, as well as annual bone density measurements [35]. It has been suggested, however, that the NIH criteria for parathyroidectomy in asymptomatic patients are too limited and that all patients with primary HPTH should be referred for surgical therapy [37, 38].

There is no long-term effective pharmacologic treatment for primary HPTH. There are several pharmacologic agents that can transiently lower the serum calcium level (Table 35.4). These can limit further loss of bone by reducing the activation of new remodeling units in the skeleton. Estrogen replacement, salmon calcitonin, bisphosphonates, and more recently, calcimimetics (cinacalcet) have been used to treat primary HPTH in patients with complex comorbid medical conditions, either unwilling or considered unfit for surgery. In addition, glucocorticoids and calcimimetics can be employed during refractory hypercalcemia of metastatic parathyroid carcinoma [25, 27]. In the geriatric population, particularly in elderly postmenopausal women, it has been demonstrated that estrogen replacement therapy combined with either calcitriol or calcium supplements, appeared as effective as parathyroidectomy for the treatment of osteoporosis in the setting of primary HPTH [39–41]. In addition, the combination of calcitriol and calcium may be effective in reducing systolic hypertension associated with HPTH [42, 43]. However, these therapies are not definitive; with adequate preoperative parathyroid localization, experienced parathyroid surgeons may employ minimally invasive techniques with good outcomes in the elderly population [44].

Parathyroidectomy without preoperative localization studies has a high success rate (>95%) and a low complication rate. Complications associated with parathyroidectomy

Table 35.3 Surgical indications in patients with primary hyperparathyroidism

All symptomatic patients, including those with significant bone, renal, gastrointestinal, or neuromuscular symptoms typical of primary hyperparathyroidism
In otherwise asymptomatic patients:
Elevation of serum calcium by 1 mg/dl or more above the normal range (i.e., >11.5 mg/dl in most laboratories)
Marked elevation of 24-h urine calcium excretion (e.g., >400 mg)
Decreased creatinine clearance (e.g., reduced by >30% compared with age-matched normal person)
Significant reduction in bone density of more than 2.5 standard deviations below peak bone mass at any measured site (i.e., *T*-score <2.5)
Consistent follow-up is not possible or is undesirable because of coexisting medical conditions
Age younger than 50 years

Source: Modified from [30]. Copyright Elsevier (1994)

Table 35.4 Pharmacologic treatment for primary hyperparathyroidism

Pamidronate/bisphosphonates	
Dosage	60–90 mg as a single dose
Adverse effects	Leukopenia, fever, and myalgia
Contraindications	Hypersensitivity
Special points	Onset 1–2 days with long half-life
Chronic oral sodium phosphates	
Dosage	1–3 g daily
Adverse effects	Extraskeletal calcifications
Contraindications	Serum calcium > 12 mg/dl, serum
Special points	phosphorus > 3 mg/dl
	Not indicated in acute hypercalcemia
Calcitonin	
Dosage	4–8 U/kg every 6–12 h
Adverse effects	Nausea, glucose intolerance
Contraindications	Allergic reactions
Special points	Effective within 2 h; can be used to lower serum calcium while awaiting effect of bisphosphonates
Furosemide	
Dosage	20–40 mg up to three times daily
Adverse effects	Electrolyte imbalance
Contraindications	Anuria, hepatic coma, and hypovolemia
Special points	Hydration is essential
Cinacalcet*	
Dosage	30–90 mg daily
Adverse effects	Nausea, vomiting, diarrhea
Contraindications	Hypersensitivity, and hypocalcemia
Special points	*Off-label use in primary HPTH except parathyroid carcinoma

include recurrent laryngeal nerve injury, transient or persistent hypocalcemia, postoperative hemorrhage, and pneumothorax [45]. Despite this, the specific operative approach has continued to evolve through the influence of a number of synergistic factors, including improvements in preoperative localization studies as mentioned above, rapid intraoperative PTH measurements, and adjunctive surgical technologies such as hand-held gamma detection probes and small videoscopic equipment. The net result has influenced patient selection so that the majority of parathyroid explorations are very well tolerated. However, difficult explorations remain difficult. Therefore, any surgeon performing parathyroidectomy must be facile and comfortable with standard four-gland parathyroid exploration. In fact, experienced parathyroid surgeons today achieve cure rates of up to 98% with both minimally invasive and conventional techniques [46].

The conventional technique for parathyroid exploration requires a bilateral cervical exploration. This operation is usually performed under general anesthesia, although it can be performed under bilateral regional superficial cervical block [47]. The goal is to identify all normal and abnormal parathyroid glands, thus distinguishing single-gland from multigland disease. Patients who have a single parathyroid adenoma undergo curative resection once the gland is removed. In the instance of multigland hyperplasia, a subtotal parathyroidectomy (leaving a remnant of one well-vascularized parathyroid gland in situ) is required. Total cervical parathyroidectomy with immediate heterotopic transplantation of parathyroid tissue is less desirable for patients with sporadic HPTH, but often is employed in the setting of familial HPTH, such as MEN-1.

The conventional approach has been challenged with increasing frequency in recent years, and minimally invasive parathyroid exploration is now performed routinely in several institutions. Three techniques have emerged: image-guided local exploration, most often in conjunction with intraoperative PTH assays; intraoperative gamma probe-guided exploration after sestamibi injection; and, image-guided video parathyroidectomy.

Image-guided local exploration has emerged as the most commonly employed minimally invasive technique. It is dependent on high-quality preoperative imaging, usually in the form of sestamibi scans, ultrasound studies, or, less commonly, CT scans. This technique is appropriate even for patients who have had multiple previous explorations, as long as the preoperative imaging is adequate [48, 49]. When performed by an experienced parathyroid surgeon well-versed in minimally invasive techniques, this surgical procedure can be performed on an outpatient basis and can avoid the risks of bilateral neck exploration and general anesthesia [50, 51]. This technique has become particularly more favorable for elderly patients with primary HPTH and additional comorbidities; these patients often are denied referral for parathyroidectomy because of the associated risks of general anesthesia and bilateral neck exploration. Studies have shown that minimally invasive parathyroidectomy can be performed safely and can facilitate clinical care in these high-risk patients [52, 53].

Gamma probe exploration involves preoperative administration of ^{99m}Tc-sestamibi to localize the abnormal parathyroid gland. The probe is then used in the operating room to find the area of increased radioactivity. In addition, the gamma probe can be used to measure radioactivity after tumor extraction to confirm the adequacy of resection. Although this technique has not gained widespread acceptance, the curative rates are comparable to the previously described technique [54].

Image-guided video parathyroidectomy has been employed by several investigators. Like the other minimally invasive techniques, preoperative imaging is required to locate the adenoma. The procedure usually requires general anesthesia with or without carbon dioxide insufflation to aid the dissection [55]. There may be very select patients in whom this technique is indicated. However, it is not a common procedure in elderly patients, as it offers no additional benefits for this specific patient population. This technique has not assumed a dominant role in parathyroid surgery in the US.

Clinical Outcomes

In the hands of an experienced parathyroid surgeon, it has been demonstrated that patients who underwent either conventional bilateral neck exploration or minimally invasive parathyroidectomy had equivalent cure rates. The rationale for parathyroidectomy is supported by evidence that in about 80% of patients, the clinical manifestations of primary HPTH improve after successful parathyroidectomy. Thus, fatigue, weakness, polydipsia, polyuria, bone and joint pain, constipation, nausea, and depression improve in most patients. This is also true for associated conditions – new renal stones usually stop forming, osteoporosis stabilizes or improves, pancreatitis becomes less likely, and peptic ulcer disease often resolves. In most patients, fracture risk and weakness also improve, and objective increase in muscular strength has been documented [56–60]. In addition, neurocognitive impairments, confusion, spatial learning deficits, and depression have been shown to improve after successful operative intervention. Patients can resume a regular diet with or without calcium supplementation, and hypercalcemia is not a concern when these patients are hospitalized for other medical conditions [61–65].

However, there is a natural reluctance to subject elderly patients to an operation when the advantages are less clear. Advances in parathyroid imaging resulting in a greater use of targeted or focused parathyroidectomy has opened the way for the inclusion of less fit patients into the potentially operable category. Chen et al. compared demographic and outcome data of elderly patients (>70 years of age) to those of

younger patients (<70 years of age); and found that mental impairment, bone disease, and fatigue were more common in elderly patients, and nephrolithiasis was more frequent in younger patients. Elderly patients presented with more advanced disease, manifested by higher preoperative PTH levels. However, the cure rate, morbidity, and mortality in the elderly were indistinguishable from those of their younger cohorts [66]. Similarly, Bachar et al. found that there was no practical difference in perioperative management and surgical outcomes for patients over the age of 70 years, and concluded that surgeons should consider parathyroidectomy in primary HPTH patients regardless of age [67].

Several quality-of-life studies have been performed using standardized tools such as the SF-36 health survey in patients with primary HPTH, and have demonstrated that patients experience an improvement in health status and quality of life after operative correction [68, 69]. Furthermore, this benefit was independent of preoperative calcium levels [70]. Psychological distress, as measured by the General Health Questionnaire, has also been shown to be ameliorated by parathyroidectomy [71, 72]. The Parathyroid Assessment of Symptoms (PAS), a patient-based outcome tool, was developed specifically for patients with primary HPTH. A multicenter study using this questionnaire indicated that PAS is a reliable measure of the symptoms associated with HPTH, and that these symptoms improve after parathyroidectomy [73].

Both classic and more subtle clinical manifestations of primary HPTH warrant medical evaluation and, in most patients, parathyroidectomy. This especially is true when parathyroidectomy is performed by an experienced parathyroid surgeon, with a success rate greater than 97% and a very low complication rate. Furthermore, with the advent of minimally invasive techniques, these operations can often be done on an outpatient basis. Elderly patients are an especially vulnerable population, and should be referred to experienced parathyroid surgeons who have the knowledge, skill and available technology to perform these surgeries in minimally invasive fashion, with faster intraoperative times, less anesthetic requirements and low operative complications.

For patients with severe bone disease, often evidenced by markedly elevated preoperative blood alkaline phosphatase levels, subsequent "bone hunger" often necessitates postoperative treatment with calcium supplementation and calcitriol [56]. Normocalcemia generally is restored within the first 24 h after a successful parathyroidectomy, and this may be accompanied by mild paresthesia in the extremities. Symptoms may occur while the serum calcium level is within the normal range, reflecting the rapidity of change; however, this is usually transient and does not require treatment. Symptomatic hypocalcemia is more common in the elderly, in those with more severe preoperative HPTH, or in patients with evidence of high-turnover bone disease. Elderly patients may be magnesium deficient, and this may lead to a functional hypoparathyroidism, which can be corrected by magnesium supplementation. Restoration of normocalcemia can be achieved with calcitriol in combination with supplemental calcium. It is sufficient to maintain the serum calcium within the lower part of the reference range in order to control symptoms. This also provides a greater margin of safety from hypercalcemia, which may be a particular risk in elderly patients with renal impairment [74].

Another and perhaps more important reason for recommending parathyroidectomy is that patients with primary HPTH appear to be at risk for premature death primarily because of cardiovascular disease and cancer, as documented by Palmer et al. and confirmed by Hedback et al. [75, 76] More importantly, the increased death rate, even in patients with mild primary HPTH, can be reversed by successful parathyroidectomy. Patients between the ages of 55 and 70 years seem to receive the greatest survival benefit.

Secondary and Tertiary Hyperparathyroidism

In contrast to the intrinsic feedback inhibition defect of primary HPTH, secondary HPTH is caused by chronic extrinsic overstimulation of otherwise normal parathyroid glands (Fig. 35.4a, b). Although it may result from malabsorption syndromes, celiac disease, or extreme dietary calcium or vitamin D deficiency, secondary HPTH occurs most commonly in the setting of chronic renal insufficiency associated with renal osteodystrophy. The stimulus for PTH hypersecretion is a reduced extracellular calcium concentration and reduced endogenous calcitriol production that is associated with reduced renal function [77, 78].

Tertiary hyperparathyroidism refers to the development, in the setting of longstanding secondary HPTH, of autonomous hypersecretion despite correction of the underlying case of PTH stimulation. This may be suspected when an individual with documented secondary HPTH develops refractory hypercalcemia, or after renal transplantation in a previously dialysis-dependent patient [79].

The distinction between secondary and tertiary HPTH is not critical when considering surgical intervention because refractoriness to medical therapy in secondary HPTH is functionally equivalent to the intrinsically refractory autonomy seen in tertiary HPTH. The indications and rationale for surgical therapy are the same. Elderly patients with renal disease are prone to severe bone loss, and seem to benefit from parathyroidectomy [78].

Clinical and Diagnostic Evaluation

Patients with chronic renal failure (CRF) have considerable morbidity and mortality. Classic clinical manifestations of worsening secondary HPTH are related to osteodystrophy

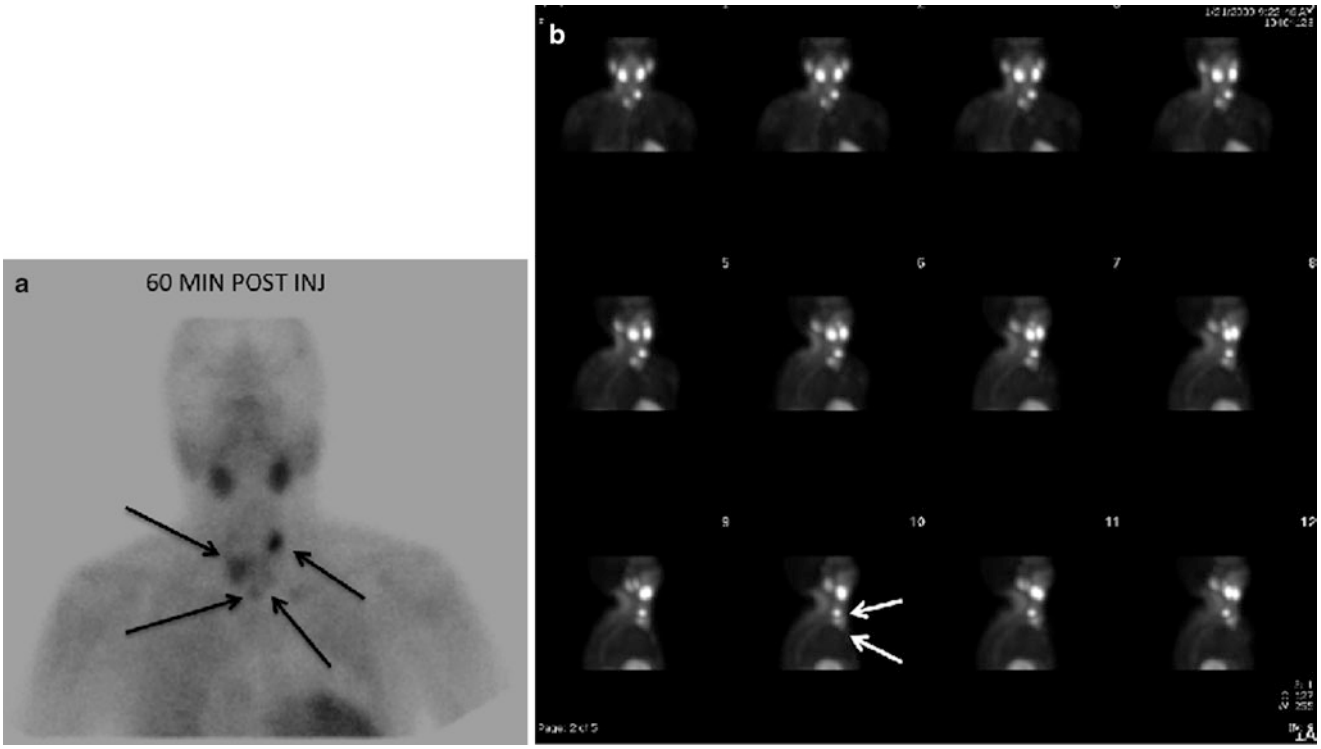

Figure 35.4 (**a**) Scintigraphic image from ^{99m}Tc-sestamibi depicting four-parathyroid-gland activity (*arrows*) in tertiary hyperparathyroidism. (**b**) Scintigraphic images from sestamibi single-photon-emission tomography of the same patient presented in Fig. 35.4a depicting multiple rotational tomographic planes. The right superior and inferior parathyroid glands (*arrows*) are visualized on sagittal view.

(pain, deformities, and fractures), extraskeletal calcifications, and the skin (pruritus and calciphylaxis).

Changes in bone structure due to secondary HPTH are common and begin early in the course of CRF. Renal osteodystrophy includes two major pathologies: osteitis fibrosa cystica and adynamic bone disease. In mixed osteodystrophy, features of both osteitis fibrosa and decreased mineralization coexist. The form and severity of the bone disease depend on the gender and age of the patient; the severity and duration of the CRF; metabolic acidosis; the characteristics of dialysis; calcitriol and PTH levels; dietary calcium and phosphate load; additional medications, particularly steroids; and associated endocrine diseases, such as diabetes mellitus. In addition, parathyroidectomy and renal transplantation can modify acutely the precarious balance of long-deranged mineral metabolism [80].

A disease of high bone turnover, osteitis fibrosa cystica is a consequence of elevated PTH secretion and is characterized by increased osteoclasts, osteoblasts, osteocytes, and fibroblasts. There is a correlation between the serum PTH level and the rate of bone turnover; and the probability of high-turnover bone disease increases with rising serum PTH concentrations. Serum PTH greater than 450 pg/ml is closely related to high-turnover bone disease in hemodialysis and peritoneal dialysis patients. It has become possible to suppress PTH secretion with the administration of calcium and vitamin D; therefore, the frequency of classic osteitis fibrosa and mixed forms is decreasing, while the frequency of adynamic bone disease is increasing [81].

In contrast to osteitis fibrosa, adynamic bone disease is associated with low levels of serum PTH. This disease is characterized by unequal decreased numbers of both osteoclasts and osteoblasts, with a predominant deficiency of osteoblasts. Low bone formation rates lead to decreased bone mass [17, 81]. In the past, adynamic bone disease also was associated with high aluminum dialysis baths, but this has become less pronounced with modern dialysates.

There are three types of extraskeletal calcifications (systemic calcinosis): visceral, periarticular, and vascular. Visceral calcifications may involve the lungs, breast, myocardium, mitral valve, kidneys, and skeletal muscle. Patients often have hyperphosphatemia, an elevated calcium-phosphorus product, and increased PTH levels. Periarticular calcification or tumoral calcinosis results in calcific periarthritis and small-joint effusions; radiographically, calcifications can be seen around the joint. Vascular calcifications of both large and small vessels occur in 20% of patients with CRF, and may cause falsely elevated blood pressure measurements. Parathyroidectomy rarely affects vascular calcification, but usually diminishes nonvascular calcium deposits [82, 83].

The skin manifestations associated with secondary HPTH include pruritus and calciphylaxis. Pruritus affects up to 85% of hemodialysis patients. Although dramatic improvement of

pruritus has been observed after parathyroidectomy, PTH does not seem to be directly involved in its pathogenesis. Rather, abnormal serum levels of phosphate, calcium, and magnesium may cause pruritus [84].

Calciphylaxis, or calcific uremic arteriolopathy, a rare syndrome of disseminated calcification, is a severe complication of secondary HPTH, and results in soft tissue calcification, vascular medial calcinosis, and arteriolar thrombosis leading to ischemic tissue necrosis. Patients present with painful, violaceous, mottled lesions that may progress to skin and subcutaneous tissue necrosis, nonhealing ulcers, and gangrene. Lesions are characteristically located in the hands and fingers, lower extremities, and occasionally lower abdomen. Patients usually have a high calcium-phosphate product, but not necessarily highly elevated PTH levels. The prognosis generally is poor, particularly in patients with truncal and proximal extremity lesions, with mortality approaching greater than 50%. When symptoms and signs of calciphylaxis are identified, the patient should be treated with phosphate binders and timely parathyroidectomy [85, 86]. Necrotic skin ulcers should be treated with standard wound care, debridement, and avoidance of superinfection. For large, non-healing ulcers, hyperbaric oxygen therapy has been employed with mixed results. Sodium thiosulfate has been shown to produce clinical improvement of calciphylaxis lesions. Bisphosphonates have been shown to be effective in animal models of calciphylaxis, and the mechanism of action is believed to be due to inhibition of macrophages and local proinflammatory cytokines as well as binding to calcified vascular smooth muscle cells to inhibit further arterial calcification. Cinacalcet is thought to decrease serum PTH levels and stabilize calcium and phosphate concentrations, and has been associated with improved pain control and ulcer healing. Calciphylaxis remains a poorly understood disease, as most of the data on these therapies consist of case reports [87].

Tertiary HPTH occurs most commonly following renal transplantation in a previously dialysis-dependent patient. Symptoms resemble those of primary HPTH and may include increased bone resorption, nephrolithiasis, and pancreatitis. Increased bone resorption is often exacerbated by preexisting osteodystrophy, and steroid-induced osteopenia. Tertiary HPTH is the main cause of nephrolithiasis in transplanted kidneys, presenting as painless hematuria in the grafted denervated kidney. Pancreatitis, which occurs in 2–6% of kidney transplant recipients, has a prevalence of 11% in those with hypercalcemia [88–90].

Treatment

The initial management of secondary and tertiary HPTH revolves around medical therapy with or without dialysis in order to maintain a stable mineral milieu. This therapy focuses on dietary phosphate restriction, vitamin D sterols, and calcimimetics [91].

Phosphate retention represents one of the major factors in the development of secondary HPTH. The first step to control serum phosphorus is to reduce phosphate intake. However, the extent of dietary phosphate restriction is limited by malnutrition associated with inadequate protein intake and often, poor patient compliance. Thus, the use of phosphate binders is required in almost all patients, particularly those who are dialysis-dependent. Phosphate binders can be calcium-based, aluminum-based, or neither calcium- or aluminum-based; the choice is dependent on the patient's calcium level [91].

After achieving the desired serum phosphorus levels with dietary restriction and the use of binders, secondary HPTH may often persist due to vitamin D deficiency. In this case, vitamin D should be substituted. Calcitriol is the most active metabolite of vitamin D; however, in the setting of CRF, there are potential adverse effects. Calcitriol promotes the intestinal absorption of calcium and phosphate, leading to hypercalcemia and hyperphosphatemia, with a subsequent rise in calcium-phosphate product, a known risk factor of mortality in CRF. In addition, oversuppression of PTH secretion can lead to adynamic bone disease and may, in turn, further aggravate hypercalcemia and hyperphosphatemia. Therefore, vitamin D should not be administered until the serum phosphorus is under adequate control. Several vitamin D analogs have been developed that retain a suppressive action on PTH and parathyroid gland growth with concomitantly less calcemic and phosphatemic activity. These include paricalcitol, doxercalciferol, and maxacalcitol [92].

The parathyroid CaSR regulates PTH secretion. In secondary HPTH there is underexpression of the CaSR, leading to partial loss of calcium-regulated PTH suppression. Calcimimetics allosterically modulate the CaSR, thereby sensitizing it to extracellular calcium ions. The reestablished calcium sensitivity leads to the suppression of PTH production. In contrast to vitamin D sterols, which show an effect on PTH levels in hours or days by inhibition of PTH synthesis, the modification of the CaSR and the resulting inhibition of PTH secretion leads to changes in serum PTH in minutes to a few hours. The advantage of calcimimetics, like cinacalcet hydrochloride, is the capacity to suppress PTH secretion with concomitant rise in serum calcium and phosphorus [93].

Parathyroidectomy is indicated when medical treatment fails to control progressive secondary HPTH. Clinical manifestations include persistence or worsening of skeletal symptoms, pruritus, and extraskeletal calcifications. Elevated intact PTH levels and a proven high-turnover bone disease are prerequisites for consideration of surgery. Calciphylaxis is an indication for immediate parathyroidectomy (Table 35.5) [86].

Indications for operative intervention in tertiary HPTH are similar to those of primary HPTH, namely, significant hypercalcemia, decline in creatinine clearance, nephrolithiasis,

Table 35.5 Indications for parathyroidectomy in secondary hyperparathyroidism

Appropriate medical treatment and elevated PTH levels and high-turnover bone disease with any of the following:
Bone pain that is disabling or dependent on continuous analgesic drugs
Pathologic fractures
Subperiosteal resorption documented on plain radiographic films
Hypercalcemia unresponsive to phosphate restriction and phosphate binding
Hyperphosphatemia unresponsive to phosphate restriction and binding
Severe pruritus
Extraskeletal nonvascular calcifications (systemic calcinosis)
Intractable anemia
Calciphylaxis

Table 35.6 Indications for parathyroidectomy after kidney transplantation

Subacute severe hypercalcemia
Persistent hypercalcemia and one of the following:
Deterioration of renal function
Nephrolithiasis
Progressive bone disease
Acute pancreatitis

acute pancreatitis, changes in mental status, or overt bone disease. Mild hypercalcemia alone does not appear to be a serious threat to the patient with a transplanted kidney, and its treatment remains controversial. However, impaired renal function in the presence of elevated PTH and hypercalcemia should be an indication for parathyroidectomy, especially in the elderly patients (Table 35.6) [88].

Preoperative preparation of dialysis patients includes control of hyperkalemia, hypomagnesemia, and hypervolemia with careful evaluation and treatment of hypertension and cardiovascular disease. Patients should receive oral calcitriol before surgery to avoid severe postoperative hypocalcemia. They should be dialyzed no longer than 1 day before parathyroidectomy and then again no later than 2 days after the operation. When parathyroidectomy is performed after kidney transplantation, immunosuppressive medications do not have to be interrupted in the perioperative period. However, replacement glucocorticoid doses should be administered [86–88].

The two accepted operative procedures for the management of secondary and tertiary HPTH are subtotal parathyroidectomy and total parathyroidectomy with immediate parathyroid autotransplantation [94]. The variability of the number of parathyroid glands is well known; in a report on 519 patients undergoing total parathyroidectomy with parathyroid forearm autotransplantation, supernumerary glands were found in 14.5% of patients. The most frequent location of supernumerary glands (39%) was the thymic tongue [95, 96]. Thus, transcervical thymectomy is performed routinely to decrease the risk of recurrent HPTH and to lower the rate of reoperations to the neck [97, 98].

Intraoperative PTH measurement is an established tool in determining the successful removal of parathyroid tissue in patients undergoing surgery for primary HPTH. Recent studies have provided evidence that intraoperative PTH monitoring also may be useful during surgery for secondary and tertiary HPTH. After subtotal or total parathyroidectomy, an appropriate and rapid decline of PTH levels is expected. A persistent elevated PTH, however, can result from non-identified supernumerary glands, and further identification and removal of additional parathyroid glands are indicated [99, 100].

Clinical Outcomes

The overall clinical result is considered good in 70–85% of patients who undergo successful parathyroidectomy. In a few days, bone pain improves in 60–80%, malaise in 75%, and joint pain in 85% of patients. Muscle weakness is alleviated in one third of the patients with improvement of radiologic signs in 95%. Pruritus decreases overnight in almost all patients and disappears in 60–80% [101].

Successful parathyroidectomy improves nonvisceral calcifications in 50–60% of patients. However, it does not change arterial calcification despite reduction in the calcium-phosphate product and PTH. Small peripheral arterial calcification may progress or even develop in approximately 56% of patients after operative intervention [101].

Conclusion

Hypercalcemia is a common finding in the elderly population. It appears to have widely encompassing effects on many aspects of geriatric health, from cognitive and psychiatric decline to diminished function of the cardiovascular, renal, bone, endocrine, and gastrointestinal systems. It may be associated with underlying malignancy, but concomitant intact PTH measurement usually is diagnostic. HPTH peaks in the fifth decade of life, but elderly patients are at increased risk to develop HPTH. Such patients should be evaluated carefully, and surgical interventions, when appropriate, should be undertaken by experienced parathyroid surgeons. With the advent of better imaging studies and minimally invasive operative techniques, elderly patients who may have been considered poor surgical candidates can now undergo safe and successful parathyroidectomy with improved health status, enhanced quality of life, and prolonged life expectancy.

CASE STUDY RESOLUTION

After appropriate medical management of acute hypercalcemia, including intravenous hydration, bisphosphate and furosemide therapy, the patient's serum calcium decreased to 10.8 mg/dL and her mental status returned to baseline. She underwent a sestamibi scan with SPECT, which revealed increased uptake in the right inferior anterior neck. After adequate medical evaluation, she underwent a minimally invasive parathyroidectomy with excision of a right inferior parathyroid adenoma. Intraoperative rapid PTH measurement documented adequate resection with a decline from her baseline 200 to 35 pg/ml at 10 min post-resection. The patient returned home the following day with a normal serum calcium level of 9.8 mg/dL, and a post-operative regimen of oral calcium supplementation. At 6 months post-operatively, she remained eucalcemic and did not have any further episodes of nephrolithasis.

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