Diagnosis and Management of Endocrine Disorders in Interventional Radiology

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Springer

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Preface

Diseases of the endocrine system involve an imbalance in the natural homeostasis of the hormones produced by the glands in the body. There are a variety of endocrine conditions characterized by either hormonal hyposecretion or hypersecretion. Often, these conditions can lead to debilitating or, in some instances, life-threatening situations that can be challenging to diagnose and treat. While one doesn't often consider interventional radiology a critical part of the endocrine clinic setting, there are several conditions for which interventional radiologists can play a valuable role. These disorders include primary aldosteronism, primary hyperparathyroidism, Cushing's disease, hormone-secreting pancreatic adenomas, and androgen-secreting ovarian tumors. A collaboration of multiple specialties, including endocrinologists, surgeons, and radiologists, is often needed to diagnose and manage these conditions.

Radiologists play a prominent role in the evaluation of patients with suspected endocrine disorders. CT and MRI are commonly used first-line imaging modalities; however, cross-sectional imaging lacks physiologic information resulting in poor specificity of these tests for many endocrine conditions. Thus, percutaneous selective venous sampling is a useful diagnostic tool for the medical and surgical management of patients with select endocrine disorders. Selective venous sampling is a minimally invasive interventional procedure performed by interventional radiologists to localize sites of abnormal hormone secretion. These tests can confirm a suspected clinical diagnosis and, in some instances, direct curative surgical therapy.

As venous sampling procedures are increasingly performed worldwide, the collaboration between interventional radiology, endocrinology, surgical endocrinology, surgical oncology, neurosurgery, and gynecology teams is essential. Currently, there are limited guidelines from The Endocrine Society and relatively few published papers for each venous sampling procedure. Furthermore, except for the book "Percutaneous Venous Blood Sampling in Endocrine Diseases" published in 1992 by Springer, there is no modern comprehensive guide for all traditional and newly emerging selective venous sampling procedures.

To correct this information gap, we have put together a book focusing on selective venous sampling, including the interventional techniques for diagnosis and chapters on the pathophysiology, epidemiology, clinical diagnosis, and medical,

surgical, and interventional treatments of endocrine disorders. We have recruited experts from endocrinology, endocrine surgery, radiology, and interventional radiology to provide a comprehensive and state-of-the-art textbook surrounding the diseases in which venous sampling is typically used. We have also included chapters on the latest percutaneous therapies that may be the future for treating some common endocrine disorders, such as hyperthyroidism and hyperparathyroidism. And given the rise in pediatric interventional radiology in recent years, we felt it was important to dedicate a chapter to venous sampling in this patient population.

This book is organized into five parts: Clinical, Laboratory, and Radiological Diagnosis, Selective Venous Sampling, Medical and Surgical Management, and Intervention Treatments, with chapters in each part addressing primary aldosteronism, hyperparathyroidism, hyperandrogenism, hypercortisolism, and pancreatic islet cell tumors. This type of organization allows the reader to read the book straight through to get a comprehensive overview from the initial evaluation through the different management options for these disease processes. Alternatively, the reader can select specific chapters to answer a particular question or focus on a single disease process.

As interventional radiologists, we have experienced firsthand the value and complexity that venous sampling procedures can provide. These procedures can be gratifying and significantly improve patient care. Understanding the relevant disease processes from the perspective of the other members of the multi-disciplinary teams and learning the selective venous sampling techniques from the experts will help guide the interventional radiologist to be a more valuable team member. We have thoroughly enjoyed the process of bringing this book together, and we hope that all readers who are involved in the management of these patients will find this book a valuable reference for many years.

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The original version of this book was revised: The incorrect author affiliation has been corrected. The correction to this book can be found at https://doi.org/10.1007/978-3-030-87189-5_22

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Part I
Clinical, Laboratory, and Radiological Diagnosis of Endocrine Disorders

Chapter 1
Clinical, Laboratory, and Radiological Diagnosis of Primary Aldosteronism

Ali Qamar and Lauren M. B. Burke

Introduction

Primary aldosteronism (PA) is the most common [1] cause of secondary hypertension. Despite its relatively high prevalence, it is commonly underdiagnosed. Patients with untreated PA have an increased risk of stroke, atrial fibrillation, heart failure, coronary artery disease [1], and chronic kidney disease [2] when compared to patients with essential hypertension. Aldosterone-producing adenoma and bilateral idiopathic hyperplasia are the most common subtypes of PA. Familial hyperaldosteronism is rare and will not be discussed in detail.

History

Dr. J.W. Conn was a Professor of Medicine at the University of Michigan. His research focused on the mechanisms of human acclimatization to humid heat [3]. He concluded that the body's acclimatization involved rapidly diminishing renal salt and water loss. He suggested that these responses were the result of the increased adrenocortical function of salt-retaining steroids as intramuscular administration of

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deoxycorticosterone acetate (DOCA) produced similar changes in the electrolyte composition of urine, sweat, and saliva.

In April 1954, he saw a 34-year-old woman with a 7-year history of muscle spasms, temporary paralysis, tetany, and weakness and a 4-year history of hypertension. She was found to have a blood pressure of 176/104 mm Hg, severe hypokalemia (1.6 to 2.5 mEq/L), mild hypernatremia (146 to 151 mEq/L), and alkalosis (serum pH 7.62). Because there were no signs or symptoms of glucocorticoid or androgen excess, Dr. Conn suspected that her clinical presentation was related to adrenal salt-retaining corticoid [4] and studied DOCA level in the patient's urine which averaged 1333 μg/day equivalent compared with normotensive control subjects who averaged 61.4 μg/day.

In December 1954, his study patient was scheduled for bilateral adrenalectomy, but surgeons found a 13-g right adrenal tumor which was removed while leaving the contralateral gland intact. "The patient's postoperative studies showed an almost total reversal of the preoperative metabolic and clinical abnormalities. Conn had achieved irrefutable proof of the validity of his investigative conclusions and established for the first time the relationship between an adrenal aldosterone-producing tumor and hypertension with hypokalemia. A new era had arrived in the study of hypertension and adrenal mineralocorticoids" [5].

In his Presidential Address Primary aldosteronism (PA) history to the 1955 Society of Clinical Research, Dr. Conn stated: "It is believed that these studies delineate a new clinical syndrome which is designated *temporarily* as Primary Aldosteronism" [4].

Prevalence

Historically, the diagnosis of PA was not considered unless a patient had spontaneous hypokalemia, and then the diagnostic evaluation would require discontinuation of antihypertensive medications for at least 2 weeks. This resulted in predicted prevalence rates of less than 0.5% of hypertensive patients. Based on the available literature review, most patients with PA are not hypokalemic, and screening can be completed while the patient is taking antihypertensive drugs. Current prevalence estimates for PA suspect the diagnosis in 5–10% of all patients with hypertension [6–8]. Recently published data from four US academic centers showed a high prevalence of biochemically overt PA that parallels the severity of hypertension [9].

Hypokalemia and Primary Aldosteronism

Only 9–37% of patients with PA have hypokalemia [10, 11], and the absence of hypokalemia in no way should deter clinicians from screening for primary hyperaldosteronism. The prevalence of target-organ damage to the heart and kidney is increased in patients with PA compared to those with essential hypertension [1].

Case Detection: Who Should Be Tested?

The Endocrine Society guidelines for PA recommend case detection in the following patients [11]:

1. Blood pressure over 150/100 on three measurements on different days
2. Uncontrolled blood pressure >140/90 on three conventional drugs, including a diuretic
3. Controlled blood pressure <140/90 on four or more conventional drugs, including a diuretic
4. Hypertension and hypokalemia (spontaneous or diuretic-induced)
5. Hypertension and adrenal incidentaloma
6. Hypertension and sleep apnea [12]
7. Hypertension and a family history of early-onset hypertension or cerebrovascular accident at a young age (<40 years)
8. All hypertensive first-degree relatives of patients with PA

Of note, patients with obstructive sleep apnea for unclear reasons have a very high prevalence of primary hyperaldosteronism [12].

How to Test

Plasma aldosterone concentration (PAC) and plasma renin activity or plasma renin concentration (PRC) are measured in *a patient with seating position in the morning.*

Renin can be measured based on its enzymatic activity (PRA) or its mass (PRC).

PRA is determined by measurement of angiotensin I generation and expressed as the amount of angiotensin I generated per unit of time (e.g., ng/mL/h).

Interfering Medications

Concern about medication interference has deterred clinicians from screening for PA. Many medications can interfere with PAC, PRA, and PRC, but screening tests can be completed when patients are taking interfering medications, including mineralocorticoid receptor antagonist (MRA), angiotensin-converting enzyme inhibitors (ACEi), and angiotensin receptor blockers (ARB) as long as PRA is non-suppressed (>1) [2, 11].

MRA, ACEi, ARB, and direct renin inhibitors can potentially elevate PRC or PRA. Therefore, if PRA or PRC is suppressed, interfering medications should be held for 4–6 weeks before repeating case detection studies.

Medications like beta-blockers, calcium channel blockers, alpha-blockers, and vasodilators like hydralazine have minimal interference. Therefore, they can be used while patients are being evaluated for primary aldosteronism.

Hypokalemia should be repleted before testing. PRC can be affected by estrogen status and false-positive results on case detection testing for PA can occur when PRC is measured in women receiving estrogen-containing preparations. PRA is not affected by estrogen preparations and is the recommended screening test [13].

Lab Interpretation

Case detection testing for PA is considered positive when PRA is suppressed to <1 ng/mL/h (or PRC below the lower limit of normal) and PAC is ≥10 ng/dL [11]. PAC/PRA ratio is generally >20, and in one study, a PAC/PRA ratio more than 30 and a PA value of more than 20 ng/dL provided a sensitivity of 90%, specificity of 91%, the positive predictive value of 69%, and negative predictive value of 98% [14].

If both PAC and PRA are elevated (after stopping interfering medications), diagnosis of renovascular hypertension should be explored. If both PAC and PRA are suppressed on case detection studies, diagnosis of Cushing syndrome, Liddle syndrome, and Licorice use should be considered.

Confirmatory Testing

Most patients with positive case detection will need confirmatory testing. Only patients who have PAC > 20 and PRA below detection levels and spontaneous hypokalemia [11] can proceed with subtype classification without confirmatory testing. Confirmatory tests include oral sodium loading test, saline infusion test, fludrocortisone suppression test, and captopril challenge test [11]. Fludrocortisone suppression test and captopril challenge test are very rarely used and falling out of favor in most parts of the world.

Oral Sodium Load This is the preferred test at most centers. After controlling hypertension and hypokalemia, patients are started on a high-sodium diet (this can be accomplished by adding three 1-gram salt tablets twice a day) for 3 days. On day 3, 24-hour urine creatinine, sodium, and aldosterone, and serum electrolytes are measured. Urine sodium>200 mEq /24 h (to document adequate sodium load) and urine aldosterone >12 mcg/24 h confirm the diagnosis of PA.

Saline Infusion Test This test is used in some centers. Patients stay recumbent for at least 1 h before and during the infusion of 0.9 saline IV over 4 h, starting in the morning, usually between the hours of 8:00 and 9:30 am. PAC will fall below 5 ng/dL (140 pmol/L) in normal patients. Values above 10 ng/dL (280 pmol/L) are consistent with PA. Values between 5 and 10 ng/dl are indeterminate. This test should not be used in patients with uncontrolled hypertension, renal insufficiency, and cardiac arrhythmia. Further, patients should be monitored for hypokalemia if this test is used [11].

Radiological Diagnosis

All patients with confirmed PA should undergo testing for subtype classification [11], including computed tomography (CT) or magnetic resonance imaging (MRI) and adrenal venous sampling (AVS), if they are surgical candidates and considering surgery as a potential treatment option.

Multiphasic CT or MRI are typically first-line imaging examinations to help detect the presence of an adrenal adenoma or adrenal hyperplasia. Unfortunately, both imaging techniques have limitations. First, adenomas can be small and below the resolution of the examination [15]. Furthermore, the presence of an adenoma does not distinguish between functioning and non-functioning adenomas. Also, many adrenal glands demonstrate diffuse nodularity with increasing age and hypertension, and it can be challenging to distinguish nodular hyperplasia from a discrete adrenal adenoma [16]. For these reasons, there is a wide range in the reported sensitivity of CT and MRI, with sensitivities ranging between 40% and 100% for CT and 70% and 100% for MRI in the detection of aldosterone-producing adenomas [17].

Adrenal adenomas do have a characteristic appearance on both CT and MRI secondary to the presence of intracellular fat [18]. On unenhanced CT images, adenomas demonstrate low Hounsfield units of 10 or lower. Contrast-enhanced CT imaging obtained in portal venous phase and at 15 min can further describe the washout characteristics of the adrenal nodule with greater than 40% relative washout and 60% absolute washout indicative of an adrenal adenoma. On chemical shift MRI, there is loss of signal on out-of-phase imaging indicative of an intracellular fat component (Fig. 1.1). Unfortunately, research has not yet determined a method to further distinguish between non-functioning and functioning adrenal adenomas.

Adrenal hyperplasia, by definition, is diffuse thickening of the adrenal gland with a length greater than 5 cm and thickness greater than 10 mm [19]. The adrenal thickening can be smooth or nodular in contour (Fig. 1.2). This has been recently challenged by Lingam et al., who describe a 100% specificity and sensitivity for

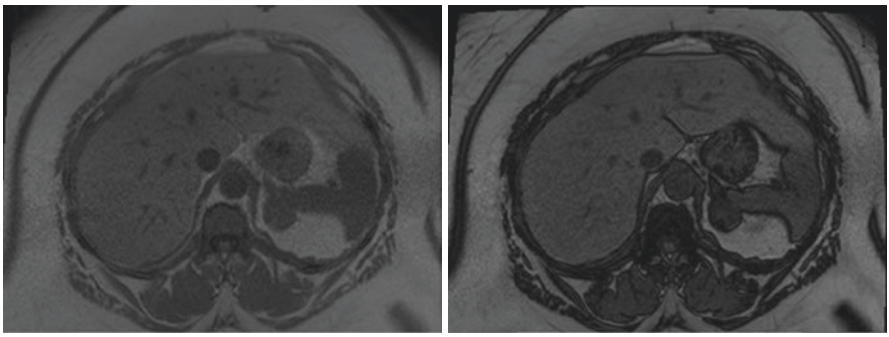

Fig. 1.1 Axial in and out-of-phase MR imaging through the upper abdomen demonstrating a 2.6 cm left adrenal nodule with loss of signal on out-of-phase imaging, compatible with intracellular lipid and an adrenal adenoma

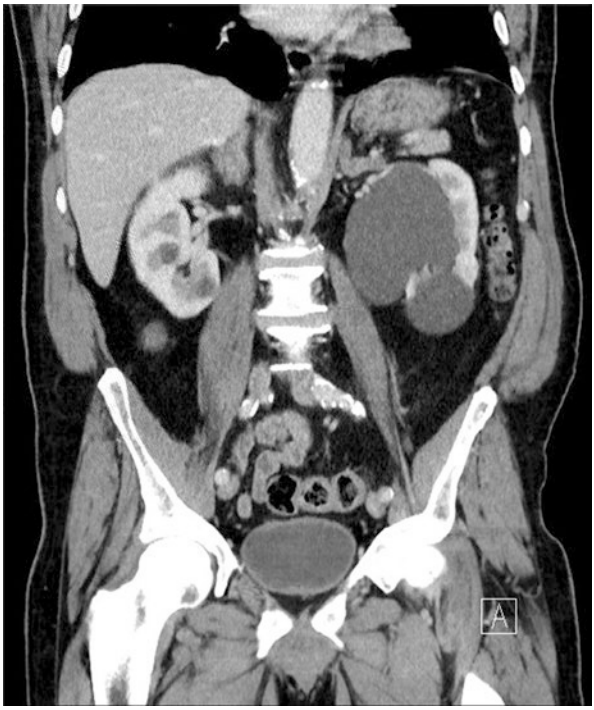

Fig. 1.2 Single coronal CT image through the mid-abdomen in portal venous phase demonstrating nodular thickening of both adrenal glands, measuring greater than 1 cm in thickness. No discrete nodule was visualized. Findings are compatible with adrenal hyperplasia

limb width greater than or equal to 5 mm and 3 mm, respectively [20]. Adrenal hyperplasia is typically a diagnosis of exclusion if no discrete adrenal nodule is detected.

Adrenal venous sampling involves obtaining blood samples from the IVC and both adrenal veins to measure aldosterone and cortisol levels and is considered the gold standard for detecting the underlying cause of PA. Specifics of this technique, including the detection rate, sensitivity, specificity, and complications, are discussed at length in Chap. 6.

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Chapter 2
Clinical, Laboratory, and Radiological Diagnosis of Hyperparathyroidism

Jennifer D. Merrill, Carlos A. Zamora, and Jorge D. Oldan

Introduction

Primary hyperparathyroidism (PHPT) is the most common cause of hypercalcemia in outpatients. It is typically characterized by a high serum calcium and high or inappropriately normal parathyroid hormone (PTH). Most PHPT is caused by a single parathyroid adenoma, but multiple parathyroid adenomas, parathyroid hyperplasia, and parathyroid carcinoma are also important causes. Although most patients present without symptoms, severe or long-standing hyperparathyroidism can cause symptomatic hypercalcemia, osteoporosis, and nephrolithiasis. A biochemical diagnosis should be confirmed before imaging studies for localization, and secondary causes of PTH elevation should be excluded. After biochemical confirmation of the diagnosis, further laboratory and imaging evaluation should center on identifying adverse impacts from the inappropriately elevated PTH. Once laboratory and imaging evaluation have confirmed the diagnosis and adverse impact from it, removal of the offending parathyroid gland is the most common treatment. Presurgical localization of the gland has allowed for the development of minimally invasive surgical techniques. Parathyroid ultrasound and SPECT-CT are the most common imaging modalities used to identify the gland and offer good sensitivity and specificity.

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Etiology

PHPT represents an autonomous spontaneous overproduction of PTH. PHPT is almost always due to a benign overgrowth of parathyroid tissue, either of single or multiple glands. Parathyroid adenomas are the most common cause of PHPT and occur in 85–90% of cases. About 5% of these patients have multiple parathyroid adenomas, and 5% have adenomas of ectopic glands. Four-gland hyperplasia and parathyroid carcinoma account for 10–15% and about 1% of PHPT cases, respectively [1–3]. PHPT caused by ectopic secretion of PTH from a non-parathyroid tumor may occur but is exceedingly rare [4].

Most cases of PHPT occur sporadically as single-gland parathyroid adenomas that are monoclonal [5], though PHPT may also occur as part of several inherited syndromes [4]. These syndromes include multiple endocrine neoplasia types 1, 2a, and 4; hyperparathyroidism-jaw tumor syndrome; and familial isolated hyperparathyroidism [4]. It is estimated that more than 10% of patients with PHPT have a mutation in one of the 11 implicated genes [6, 7].

Some of the genes responsible for heritable forms of PHPT also contribute to sporadic PHPT through a somatic mutation or a predisposing germline mutation. MEN1 and CCND1/cyclin D1 are the two molecular defects with the most established role in the pathogenesis of sporadic parathyroid adenomas [3, 4]. Cyclin D1 is a major cell cycle regulator. A pericentromeric inversion on chromosome 11 causes the relocation of cyclin D1 so that it is positioned adjacent to the PTH gene. This change causes a regulatory element of the PTH gene to cause overexpression of the cyclin D1 protein, which forces the cells to proliferate [3]. Between 10% and 20% of adenomas have this clonal gene defect, and cyclin D1 is overexpressed in approximately 40% of parathyroid adenomas [3]. Between 20% and 30% of parathyroid tumors not associated with MEN1 have mutations in both copies of the MEN1 gene [3]. Sporadic parathyroid carcinoma appears to arise through distinct pathways from parathyroid adenomas mostly. It is most frequently driven by mutational inactivation of the CDC73 (HRPT2) tumor suppressor gene, though there are many other mutations known to contribute to the pathogenesis [4].

Epidemiology

PHPT is one of the most common endocrine disorders and is the most common cause of hypercalcemia diagnosed in the outpatient setting [3, 8]. The annual incidence is estimated to be about 25 cases per 100,000 in the United States and Europe, with as many as 80% identified as outpatients by elevated calcium on routine measurement of serum electrolytes [3]. PHPT is more common in women than men, with a female to male ratio of 3–4:1 [9–11]. The demographics of PHPT vary significantly depending on whether it presents asymptomatically or as a symptomatic disease with nephrolithiasis or bone involvement. Most asymptomatic cases occur

in the 6th decade or later in life, and PHPT rarely presents before the age of 15 [3, 12]. Symptomatic patients tend to present in their 7th decade with a female to male ratio of 4:1. Patients who present with nephrolithiasis tend to present at a younger age, and females tend to predominate. In one study, patients with evidence of PHPT on skeletal radiographs at presentation presented at a mean age of 38.7 years. In this group, slightly more men presented than women [13].

Anatomy and Pathophysiology

Parathyroid Gland Anatomy

Most people have four parathyroid glands. The parathyroid glands originate in the 3rd and 4th pharyngeal pouches during embryologic development and migrate to the lower neck, which causes variation in their location [14]. About 5% of people have more than four glands, and some people only have two. The parathyroid glands typically lay external to the fibrous capsule on the posterior surface of the thyroid [15]. The superior glands are more constant in their location and are often embedded in the posterior capsule of the upper 2/3 of the left and right thyroid lobes. They may also be found in the pharynx or the tracheoesophageal groove. The location of the inferior glands is more variable due to a longer developmental migration path from the 3rd pharyngeal pouches. Almost half are located within 1 cm of the lower pole of the thyroid. They may also be found at the carotid bifurcation, in the carotid sheath, within the thymus, or near the superior portion of it, intrathyroidal, retropharyngeal, or within the thorax [16, 17].

The parathyroid glands are typically tan to reddish-brown and kidney-shaped, measuring 2–7 mm long and 2–4 mm wide and surrounded by a thin capsule [3]. They are composed of 70% chief cells and 30% fat and have a vascular supply that is anatomically distinct from the thyroid [3]. The chief cells of the parathyroid glands make PTH. Parathyroid cells have G-protein-coupled calcium-sensing receptors (CaSR) on their surface, which respond to serum concentrations of ionized calcium [18].

Parathyroid cells typically replicate during mammalian growth but rarely replicate in adulthood except when chronically stimulated by hypocalcemia, low calcitriol, hyperphosphatemia, or uremia [12, 19].

Physiologic Roles of Calcium and Organic Phosphate

Calcium and phosphorus are the main constituents of bone. Bone contains nearly all of the calcium and phosphorus in the body, but the small amounts of calcium and phosphorus in the extracellular fluid and within cells play crucial roles in normal physiologic processes [12].

Calcium has a wide range of essential intracellular and extracellular roles. Extracellular calcium serves as a cofactor for various enzymes, including the enzymes of the coagulation cascade. Calcium ions also serve as the signaling molecules for muscle contraction, neurotransmitter release, and endocrine and exocrine function [12]. Many of these functions require a large gradient between intracellular and extracellular calcium as well as tight regulation of the extracellular calcium level. About 1% of bone calcium is rapidly exchangeable with calcium in the intra and extracellular fluid. Roughly half of the calcium in the blood is bound to albumin and serum globulins. The remaining ionized fraction is biologically active and thus tightly controlled by hormonal mechanisms. A complex feedback system involving PTH, parathyroid glands, bone, kidney, small intestine, calcitonin, and parafollicular cells of the thyroid is responsible for regulating serum calcium and organic phosphate levels (Fig. 2.1).

Organic phosphate is an essential component of nucleic acids, phospholipids, complex carbohydrates, glycolysis intermediaries, a cofactor for enzymes and adenosine triphosphate (ATP). Bone contains 85% of body phosphate. Twelve percent of serum phosphate is protein bound. The intracellular and extracellular fluid contains about the same phosphate concentration [12].

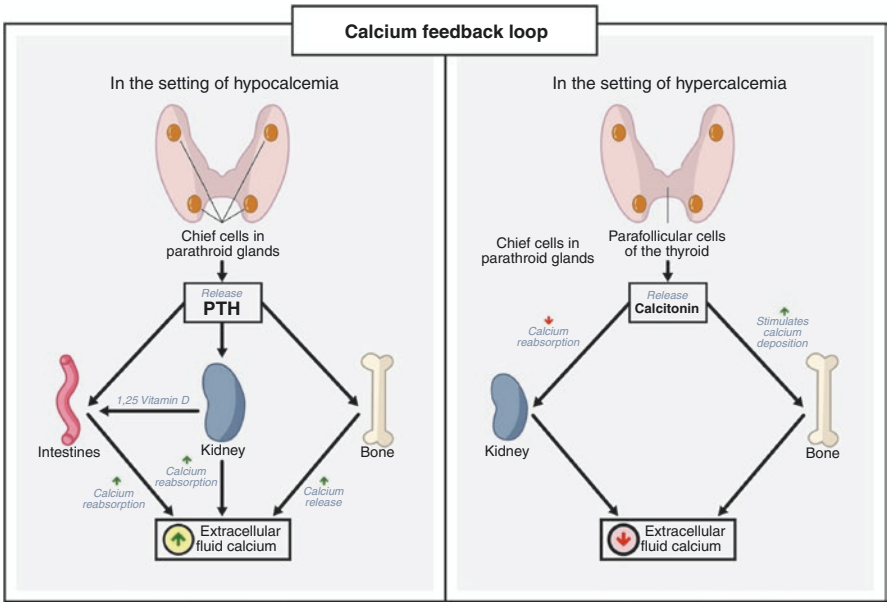

Fig. 2.1 Calcium/PTH feedback pathway. (Image courtesy of Sierra Finn, Chapel Hill, North Carolina, USA)

Regulation of Parathyroid Hormone in Response to Hypocalcemia

PTH is the peptide hormone that controls minute-to-minute ionized calcium levels in the extracellular fluid. PTH is an 84 amino acid protein that is released from the parathyroid glands when calcium is low. It exerts its effects through the interaction of its first 34 amino acids with the type 1 PTH/PTH-related peptide (PTHrP) receptor (PTHR1).

Although the major product of the chief cells of the parathyroid gland is the 84 amino acid peptide (1–84 PTH), there is considerable metabolism of this peptide, resulting in a heterogeneous assortment of circulating fragments [20]. PTH is cleaved in the liver and kidney to amino-terminal and carboxy-terminal. The amino- and carboxy-terminal fragments are present in circulation, but their clinical significance is unclear. In fact, only 5–30% of circulating PTH is the whole 84 amino acid fragment. Between 70% and 95% of circulating PTH is the carboxy-terminal fragment; the amino-terminal fragments comprise only a small percentage of circulating protein. PTH is rapidly metabolized by the liver and kidney and has a half-life of 2 min. The half-life is unaffected by serum levels of calcitriol or calcium.

Within seconds of detecting hypocalcemia by the CaSR on the parathyroid cells, the parathyroid glands release preformed PTH. PTH acts on the bone to cause calcium release and also acts on the kidney to increase calcium reabsorption and synthesis of the hormonally active 1,25-dihydroxy vitamin D (calcitriol). Calcitriol then acts on the intestine to increase the absorption of dietary calcium, as well as causing additional calcium influx from the bone and kidney. If hypocalcemia continues over the next 15–30 min, there is an increase in the net synthesis of PTH without a change in the mRNA due to decreased intracellular degradation of PTH. Within the next 12–24 h of hypocalcemia, there is an increase in the mRNA for PTH. If hypocalcemia occurs for days to weeks, the parathyroid gland cells begin to proliferate.

Increased calcitriol and ionized calcium then exert negative feedback on the parathyroid gland. Parathyroid cells respond to the absolute level of ionized calcium and the rate of fall of the calcium level. Less than 1% of the secreted hormone finds its way to the PTH receptor on the target organs.

Parathyroid Hormone Action on Bone

Skeletal release of calcium via osteoclasts occurs within 2–3 h of increased PTH release. Prolonged hyperparathyroidism causes increased number of osteoclasts, which erode bone matrix to mobilize calcium. This occurs predominantly in the metaphyses of the long bones. There is also increased activity of osteoblasts, which often results in new widely spaced delicate trabeculae [3]. In severe cases, the cortex may be thinned, and the marrow may contain increased fibrous tissue with foci of hemorrhage and cyst formation (osteitis fibrosa cystica).

Parathyroid Hormone Action on the Kidney

Almost all of the calcium filtered by the glomerulus is normally reabsorbed in the renal tubules. At least 65% is passively reabsorbed by the proximal convoluted and straight tubules through a paracellular route [21]. The remaining filtered calcium is absorbed more distally, 20% in the cortical thick ascending limb of the loop of Henle and 10% in the distal convoluted tubule and collecting tubules. The calcium transport into the cortical thick ascending limb of the loop of Henle is driven by the voltage gradient from active Na-K-Cl_2 reabsorption. Calcium absorption is inhibited by loop diuretics. The CaSR is also expressed in the cortical thick ascending limb, and it inhibits Na-K-Cl_2 reabsorption. Calcium absorption is subsequently inhibited when CaSR is stimulated by high serum calcium levels. Most of the action of PTH in the kidney is due to its impact on increasing absorption in the distal nephron. The kidney increases distal tubular calcium reabsorption in response to PTH within minutes. Renal synthesis of 1-alpha-hydroxylase and thus the production of calcitriol begin within days; this causes increased intestinal calcium absorption.

Parathyroid Hormone Action on the Intestine

Calcitriol increases intestinal calcium absorption by increasing the expression of gut lumen transport molecules. The greatest absorption is from the duodenum, but calcium is also absorbed through the entire small intestine and part of the colon.

Impact of Serum Phosphate

Hyperphosphatemia has a direct stimulatory effect on the parathyroid gland, resulting in increased PTH secretion in the short term and nodular hyperplasia of the parathyroid glands if the hyperphosphatemia is prolonged [22]. PTH also inhibits renal phosphate absorption and causes increased phosphaturia.

Clinical Evaluation

Historical Presentations

When first described in the 1920s, PHPT typically presented with severe symptoms of hypercalcemia with bone pain, spontaneous fractures, proximal muscle weakness with atrophy and hyperreflexia, gait disturbances, and nephrolithiasis [23–25]. Hyperparathyroid crisis, a discrete episode of life-threatening hypercalcemia, was also sometimes seen [25].

Current Presentation of Classic Primary Hyperparathyroidism

In the early 1970s, automated measurement of serum calcium became widespread in the United States and Europe. This allowed for routine biochemical screening of serum calcium and identifying a large number of patients without overt skeletal or renal complications [26]. In the United States and other Western countries today, the most common presentation of PHPT is a high serum calcium level identified by routine measurement in an asymptomatic individual [27, 28]. Subsequent workup will reveal concentrations of PTH elevated above the reference range, or PTH levels that are inappropriately normal in the context of hypercalcemia [29].

Overt symptoms now occur in less than 20% of patients diagnosed with PHPT [11, 30]. Nephrolithiasis is the most common overt complication of PHPT [31]. The renal stones are typically small and comprised of calcium oxalate or calcium phosphate. Renal stones and nephrocalcinosis will be seen on abdominal radiographs or renal ultrasound [24]. Even though the presentation is often asymptomatic, many PHPT patients still frequently demonstrate target organ involvement [31]. Although most asymptomatic patients are stable, progression may occur, and more than a third of patients develop nephrolithiasis, worsening hypercalcemia, or decreasing bone mineral density (BMD) at follow-up 15 years later [32]. Even mild PHPT is associated with an increased risk of vertebral, distal forearm, rib, and pelvic fractures [33].

Patients who do not have classical signs of PHPT may complain of fatigue, subjective weakness, polyuria, polydipsia, bone pain, joint pain, constipation, forgetfulness, and neuropsychiatric illness [11, 34]. There is debate about whether these symptoms can truly be attributed to PHPT, since they are common in the general population. Studies are mixed as to whether correction of PHPT resolves symptoms [35–37], though a meta-analysis suggested that parathyroidectomy yielded better quality of life and emotional well-being [38].

Normocalcemic Primary Hyperparathyroidism

Normocalcemic PHPT is now a well-recognized variant in the diagnostic spectrum of PHPT [7]. Patients present with consistently normal total and ionized calcium and elevated PTH without a clear cause for secondary elevation [6, 39]. In order to make the diagnosis, an isolated PTH level above the normal upper limit should be confirmed on several occasions over 3–6 months [7]. Disorders associated with secondary or compensatory elevations in PTH such as vitamin D deficiency, chronic kidney disease, and use of medications such as lithium, thiazide diuretics, and bone antiresorptive medication use should be excluded. Some patients with normocalcemic PHPT appear to remain stable over time without a decline in BMD. Other patients develop hypercalcemia, or other signs of PHPT with continued follow-up [40].

Laboratory Evaluation

Initial Laboratory Testing

Patients with classical hyperparathyroidism have hypercalcemia and either a PTH that is high or inappropriately normal in the setting of hypercalcemia [41]. They are often asymptomatic and referred for mild hypercalcemia on routine lab work. In severe, symptomatic PHPT, marked elevation of the serum calcium and PTH concentrations are common.

A panel of experts who have made major contributions to the understanding of asymptomatic PHPT meet regularly to make recommendations regarding the optimal management of the disease. Table 2.1 summarizes their most recent recommendations from the Fourth International Workshop, which convened in September 2013.

Table 2.1 Recommendations for the evaluation of patients with asymptomatic PHPT from the Fourth International Workshop [6]

		Notes
Recommended	Biochemistry panel	Calcium
		Phosphate
		Alkaline phosphatase
		BUN
		Creatinine
		25-Hydroxyvitamin D
	PTH	By second- or third-generation immunoassay
	BMD by DEXA	Lumbar spine
		Hip
		Distal 1/3 radius
	Vertebral spine assessment	X ray or VFA by DEXA
	24-hour urine	Calcium
		Creatinine
		Creatinine clearance
		Stone risk profile
	Abdominal imaging	X ray, ultrasound, or CT scan
Optional	HRpQCT	
	TBS by DEXA	
	Bone turnover markers	Bone-specific alkaline phosphatase activity
		Osteocalcin
		Procollagen type 1 N-propeptide
		Serum CTX or urinary CTX
	Fractional excretion of calcium on timed urine sample	
	DNA testing if genetic basis suspected	

Calcium

Corrected Calcium

Initial workup for hyperparathyroidism should include measurement of serum calcium and albumin. Calcium circulates in three distinct fractions. About 50% is the biologically important ionized fraction, 40% is protein-bound and is not filterable by the kidney, and 10% is complexed to anions. Most of the protein-bound calcium is bound to albumin, and the rest is complexed to globulins. In general, each 1 g/dL of albumin binds 0.2 mmol/L (0.8 mg/dL) of calcium [28]. The total serum calcium level should be adjusted for albumin according to the formula:

$$\text{Corrected calcium} = \text{total serum calcium in mg/dL} + 0.8 \times \left(4.0 \;\; \text{albumin in g/dL}\right)$$

Ionized Calcium

Ionized calcium can be measured in addition to corrected calcium. Ionized calcium level is a more sensitive indicator of PHPT than corrected calcium [42]. Over 20% of patients with histologically proven parathyroid disease in one study had elevation of ionized calcium but not total calcium [43]. Direct measurement of ionized calcium can be useful in situations such as extreme hyper- or hypoalbuminemia, in the setting of changing serum pH, thrombocytosis, myeloma, and Waldenstrom's macroglobulinemia [29]. Measurement of ionized calcium was not recommended by the Fourth International Workshop for Management of Asymptomatic PHPT, because many facilities do not have sufficient capabilities to rely on an ionized free calcium concentration [6]. Direct measurement of ionized calcium is limited by difficulties in accurate analysis, lack of standardization, and need for special handling [44]. Patients with normocalcemic PHPT must also have normal ionized calcium concentrations [39].

Parathyroid Hormone Assays

First Generation Assays

First-generation PTH assays are radioimmunoassays. These assays used different polyclonal antibodies directed against predominantly the mid- or carboxy-terminal portion to the PTH molecule [45]. Therefore, these assays detected predominantly PTH fragments that lacked an intact amino terminus and therefore did not activate the PTH/PTHrP receptor or mediate the hormone's actions on calcium [46]. These assays have now largely been replaced by two site immunoassays, also known as sandwich assays.