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Primary Hyperparathyroidism: Diagnostic, Imaging, and Laboratory Perspectives

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Abstract

Background: Primary hyperparathyroidism (PHPT) is a common endocrine disorder characterized by autonomous overproduction of parathyroid hormone (PTH), leading to hypercalcemia and an increased risk of renal and skeletal complications. Historically a symptomatic disease, most cases are now detected incidentally via routine biochemical screening, presenting a shift towards asymptomatic or mild presentations. However, untreated PHPT can still lead to significant morbidity, including nephrolithiasis, osteoporosis, and neuropsychiatric symptoms.

Aim: This article provides a comprehensive review of PHPT from diagnostic, imaging, and laboratory perspectives, detailing its pathophysiology, clinical evaluation, and contemporary management strategies.

Methods: A narrative synthesis of current literature and clinical guidelines is presented, covering the etiology, epidemiology, diagnostic workup (including biochemical assays and imaging modalities), and treatment options for PHPT.

Results: Diagnosis is confirmed by concurrent hypercalcemia and inappropriately elevated PTH levels, after excluding secondary causes and familial hypocalciuric hypercalcemia. Localization studies like ultrasound and sestamibi scans are reserved for preoperative planning. Management is individualized: parathyroidectomy is the only curative treatment and is recommended for symptomatic patients or those meeting specific criteria (e.g., age <50, osteoporosis, renal stones). For asymptomatic patients not meeting surgical criteria, a strategy of monitoring with regular calcium, renal function, and bone density checks is appropriate. Medical therapies like bisphosphonates, denosumab, and cinacalcet can help manage bone loss and hypercalcemia in non-surgical candidates.

Conclusion: PHPT requires a tailored approach based on symptom status, biochemical severity, and end-organ involvement. A multidisciplinary team is essential for accurate diagnosis, appropriate selection of surgical candidates, and effective long-term management to prevent complications.

Keywords: Primary Hyperparathyroidism, Parathyroid Hormone, Hypercalcemia, Parathyroidectomy, Sestamibi Scan, Osteoporosis, Nephrolithiasis.

Introduction

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Primary hyperparathyroidism is a relatively frequent endocrine disorder defined by autonomous overproduction of parathyroid hormone (PTH), leading to hypercalcemia and predisposing affected individuals to clinically significant renal and skeletal complications. Despite this potential for substantial end-organ damage, the clinical profile of the disease has shifted over recent decades, with most newly diagnosed patients exhibiting only modest elevations in serum calcium rather than the florid biochemical derangements historically described.[1] Classically, the condition was encapsulated by the aphorism “stones, bones, groans, and moans,” attributed to Fuller Albright, which emphasized the prominence of nephrolithiasis, skeletal pain, gastrointestinal distress, and neuropsychiatric manifestations. In contemporary clinical practice, however, primary hyperparathyroidism is most often detected

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incidentally through routine biochemical screening and is frequently asymptomatic at the time of diagnosis.[1] The term "stones" reflects the predisposition to nephrolithiasis and nephrocalcinosis arising from hypercalciuria, a direct consequence of PTH-driven alterations in renal tubular calcium handling. "Groans" traditionally encompass abdominal discomfort, which may include constipation, dyspepsia, or vague abdominal pain attributable to hypercalcemia-induced impairment of gastrointestinal motility. Skeletal pain may similarly be categorized under this rubric and may stem from pathological bone remodeling, microfractures, or overt osteoporosis. The "moans" of the classic description refer to the neurocognitive and affective symptoms that accompany hypercalcemia, such as lethargy, malaise, and mood disturbances. Neuropsychiatric manifestations are now recognized as part of the broader clinical spectrum of primary hyperparathyroidism and may include depression, anxiety, reduced energy, cognitive slowing, and memory impairment. Notably, various degrees of depression, anxiety, fatigue, cognitive dysfunction, and related psychological disturbances have been documented in approximately 23% of individuals with severe forms of hyperparathyroidism, highlighting the systemic and often subtle impact of this endocrine pathology.[2]

Historically, the diagnosis of primary hyperparathyroidism was usually established only after patients developed recurrent nephrolithiasis, overt bone disease, or both. Before the widespread availability of routine serum calcium measurements and bone mineral density assessment, affected individuals typically presented with advanced skeletal involvement and prominent radiological changes. Characteristic imaging findings included osteitis fibrosa cystica, which represents severe hyperparathyroid bone disease with marrow fibrosis and cyst-like lesions; so-called brown tumors, which are focal osteolytic lesions resulting from exaggerated osteoclastic activity; subperiosteal bone resorption, particularly evident along the radial aspects of the middle phalanges; "salt and pepper" demineralization of the skull; and tapering or acro-osteolysis of the distal phalanges and clavicles.[3] These radiographic features, while pathognomonic in advanced cases, are now rarely encountered in routine clinical practice due to earlier detection of the disease. The advent and widespread incorporation of bone densitometry have fundamentally altered the diagnostic approach, enabling the identification of skeletal involvement at much earlier stages. Dual-energy X-ray absorptiometry (DEXA) and related techniques can detect reductions in bone mineral density and subtle patterns of cortical bone loss long before the emergence of the dramatic skeletal deformities historically associated with untreated primary hyperparathyroidism.[3] Consequently, the contemporary clinician is more likely to encounter patients with subclinical skeletal fragility or early osteopenia rather than the overt deformities and fractures that once defined the disease.

Pathophysiologically, primary hyperparathyroidism arises from inappropriate and excessive secretion of PTH by one or more of the parathyroid glands, which are typically four very small endocrine organs located near the posterior aspect of the thyroid gland. In most individuals, these glands are situated along the posterior thyroid margins, although anatomical variation is not uncommon. Each parathyroid gland is diminutive, measuring approximately 6 mm by 4 mm and weighing only 20 to 40 mg, yet their physiological importance in calcium homeostasis is profound.[4] In primary hyperparathyroidism, one gland is most commonly affected, usually by a benign adenoma, though multiglandular hyperplasia or, rarely, carcinoma may be responsible. Definitive treatment is surgical, with parathyroidectomy representing the only curative modality, particularly in patients who are symptomatic or who meet established biochemical, skeletal, or renal criteria for intervention.[4][5][6][7] Nevertheless, for selected individuals—especially those with mild, asymptomatic disease or significant comorbidities—careful observation or medical management may be appropriate. Such conservative approaches focus on monitoring biochemical indices, renal function, and bone density, as well as mitigating hypercalcemia and its systemic effects through pharmacologic measures and lifestyle modifications.[4][5][6][7]

The regulation of PTH secretion is extraordinarily precise and is governed by a complex interplay among serum calcium, phosphorus, vitamin D, its active metabolites, and fibroblast growth factor-23 (FGF23). Serum calcium is the principal determinant of PTH release, exerting its effect through the calcium-sensing receptors (CaSR) expressed on the surface of parathyroid chief cells. Under physiological conditions, a minute decline in serum ionized calcium is detected by these receptors, leading to a rapid increase in PTH secretion, which in turn acts on bone, kidney, and indirectly on the intestine to restore normocalcemia. Conversely, elevations in serum calcium suppress PTH release via negative feedback mechanisms. Calcitriol, the active form of vitamin D (1,25-dihydroxyvitamin D), also plays a critical inhibitory role in PTH synthesis and secretion by binding to vitamin D receptors in parathyroid tissue.[4] Phosphorus may additionally modulate PTH levels, with hyperphosphatemia generally stimulating PTH secretion, although its exact role in primary hyperparathyroidism is complex and influenced by concomitant alterations in vitamin D metabolism and FGF23 signaling. FGF23, primarily produced by osteocytes and osteoblasts, contributes to phosphate homeostasis and indirectly affects PTH dynamics through its effects on renal phosphate handling and vitamin D metabolism. In

primary hyperparathyroidism, these finely tuned regulatory loops become disrupted by the autonomous behavior of the abnormal parathyroid tissue, which continues to secrete PTH despite elevated serum calcium levels. A solid grasp of normal calcium and bone metabolism, as well as the natural history of primary hyperparathyroidism, is indispensable for clinicians tasked with diagnosing and managing this condition effectively. Understanding how PTH, calcium, phosphorus, vitamin D, and FGF23 interact under physiological and pathological circumstances enables more accurate interpretation of biochemical profiles and imaging results, guides decisions regarding surgical versus conservative management, and informs long-term strategies for monitoring skeletal and renal outcomes. Ultimately, early recognition and appropriate management of primary hyperparathyroidism can prevent or substantially mitigate the renal, skeletal, and neuropsychiatric complications that historically characterized this disorder, thereby improving both longevity and quality of life for affected patients.[1][2][3][4][5][6][7]

Parathyroid Gland Physiology

The parathyroid glands are small but critically important endocrine structures whose primary function is the regulation of systemic calcium homeostasis. Histologically, the parathyroid parenchyma is composed predominantly of two principal cellular populations: chief cells and oxyphil cells.[8] Chief cells represent the most abundant and functionally significant cell type, serving as the primary source of parathyroid hormone (PTH) synthesis and secretion. They are characterized by a prominent Golgi apparatus and an extensive endoplasmic reticulum, reflecting their highly active protein-synthetic role in the continuous production of PTH.[8] Oxyphil cells, in contrast, are larger and less numerous. Their precise physiological role remains incompletely elucidated, although it has been suggested that they may possess additional endocrine properties or function in a supportive capacity that modulates or augments chief cell activity.[8] Together, these cell populations orchestrate the finely tuned hormonal responses required to maintain extracellular calcium within a narrow physiological range. The secretion of PTH is tightly and inversely regulated by the concentration of ionized calcium in the extracellular fluid through a sophisticated feedback mechanism mediated by the calcium-sensing receptor (CaSR).[9][10] The CaSR is a G protein–coupled molecular chemoreceptor located on the surface of parathyroid chief cells, and its activity fluctuates in direct response to alterations in serum calcium levels.[9][10] When extracellular calcium concentrations rise, the CaSR becomes increasingly activated, initiating intracellular signaling cascades that suppress PTH synthesis and secretion. Conversely, when serum calcium levels decline, CaSR activity diminishes, relieving this inhibitory influence and promoting an increase in PTH secretion.[9][10] This dynamic feedback loop enables the parathyroid glands to respond rapidly to even subtle changes in ionized calcium, thereby preventing the potentially harmful consequences of sustained hypo- or hypercalcemia.

Once secreted, PTH exerts its effects by binding to specific PTH receptors, primarily PTH1 receptors, expressed in target tissues such as bone and kidney. In bone, PTH stimulates osteoblastic and osteoclastic activity in a complex and context-dependent manner, ultimately enhancing the resorption of both calcium and phosphate from the skeletal matrix.[9][10] In the kidneys, PTH increases calcium reabsorption in the distal nephron, thereby reducing urinary calcium excretion under normal circumstances, while simultaneously decreasing proximal tubular phosphate reabsorption, which leads to increased urinary phosphate loss.[9][10] The net renal effect of sustained PTH elevation is therefore enhanced phosphaturia with relative conservation of calcium, at least until hypercalcemia becomes sufficiently pronounced to overwhelm the renal tubular reabsorptive capacity. At that point, hypercalcemia itself may drive increased urinary calcium loss despite ongoing PTH activity. The overall outcome of these actions is an elevation of serum calcium and a reduction in serum phosphate levels. PTH also plays a central role in vitamin D metabolism, further reinforcing its importance in mineral homeostasis. It stimulates the activity of renal 1-alpha hydroxylase, the key enzyme responsible for converting 25-hydroxyvitamin D to its biologically active form, 1,25-dihydroxyvitamin D (calcitriol).[11] This increase in calcitriol augments intestinal absorption of calcium and phosphate, thereby contributing to the restoration and maintenance of normal serum calcium concentrations.[11] At the same time, calcitriol exerts feedback inhibitory effects on PTH gene expression and secretion, adding another layer of regulation to the parathyroid–vitamin D axis. Through these interdependent mechanisms involving the parathyroid glands, bone, kidney, and intestine, PTH functions as a master regulator of extracellular calcium and phosphate balance. This integrated physiological system is highly efficient under normal circumstances, but when disrupted—whether by autonomous parathyroid overactivity, genetic receptor defects, medication effects, or malignancy-associated factors—it can give rise to various forms of hyperparathyroidism and hypercalcemia. A detailed understanding of the cellular architecture of the parathyroid glands, the molecular features of CaSR-mediated sensing, and the systemic actions of PTH is therefore indispensable for interpreting the diverse etiologies of hyperparathyroidism,

distinguishing between primary, secondary, and tertiary forms of the disorder, and guiding appropriate clinical management.[8][9][10][11]

Etiology

Hyperparathyroidism encompasses a spectrum of disorders characterized by elevated PTH activity, which may be driven by intrinsic abnormalities of the parathyroid glands or by external stimuli such as chronic hypocalcemia, medications, or malignancy. Primary hyperparathyroidism, in which excessive PTH secretion arises from one or more intrinsically abnormal parathyroid glands, is the most common etiologic category and represents the third most prevalent endocrine disorder after diabetes mellitus and thyroid disease.[12][13] The majority of patients with primary hyperparathyroidism—approximately 80%—harbor a single parathyroid adenoma, whereas around 15% demonstrate diffuse hyperplasia involving all four glands, and 2% to 4% present with multiple adenomas.[12][13] Parathyroid carcinoma, although clinically important, accounts for fewer than 1% of cases.[12][13] At the cellular level, primary hyperparathyroidism typically arises from a combination of increased clonal proliferation of parathyroid tissue and reduced expression or function of the CaSR, which together permit inappropriate PTH secretion despite elevated serum calcium concentrations.[10] While most adenomas and hyperplastic glands are located in their usual anatomical positions adjacent to the posterior aspect of the thyroid, a significant minority of hyperfunctioning parathyroid lesions occur in ectopic sites. Up to 10% of parathyroid adenomas may be found outside the typical cervical location, reflecting the complex embryologic migration of the parathyroid primordia.[14][15] Common ectopic locations include the thymus, intrathyroidal sites, the pericardium, the retro-esophageal space, and the superior mediastinum.[14][15] Even more unusual ectopic positions, such as the pharynx, the lateral neck compartments, or within the esophageal wall, have also been documented.[14][15] Recognition of these potential ectopic locations is crucial for successful surgical management, particularly in patients with persistent or recurrent hyperparathyroidism following initial neck exploration. Parathyroid carcinoma represents a rare but clinically significant cause of primary hyperparathyroidism, accounting for fewer than 1% of all hyperparathyroid cases.[16] Compared with patients harboring benign adenomas, those with parathyroid carcinoma tend to be younger at presentation and exhibit more marked biochemical abnormalities. Serum calcium levels often exceed 14 mg/dL, and PTH concentrations may reach five- to ten-fold above the upper limit of the reference range.[16] These tumors are typically aggressive and potentially life-threatening, not only due to local invasion or metastatic spread but particularly because of severe and refractory hypercalcemia, which can precipitate renal failure, cardiac arrhythmias, neurocognitive decline, and other systemic complications.[16] Although still rare, epidemiologic observations suggest that the incidence of parathyroid carcinoma may be rising in some regions, including the United States and China, underscoring the need for heightened clinical awareness and timely diagnosis.[17]

Parathyromatosis constitutes an exceedingly uncommon cause of persistent or recurrent hyperparathyroidism and is characterized by the presence of multiple small, functional nests of parathyroid tissue scattered within the soft tissues, most often in the neck or mediastinum.[18] This entity typically arises after surgical manipulation of the parathyroid glands, such as parathyroidectomy or percutaneous ablative procedures, where inadvertent seeding or implantation of parathyroid tissue can occur.[18] Patients with chronic kidney disease (CKD), who often have longstanding secondary or tertiary hyperparathyroidism and require parathyroid surgery, are particularly susceptible.[18] Parathyromatosis may mimic parathyroid carcinoma radiologically and grossly, as the small nodules are frequently embedded in dense, fibrotic postsurgical tissue. However, careful histopathological evaluation distinguishes parathyromatosis from malignancy based on the absence of invasive growth patterns and cytologic features of carcinoma.[18] A second, less common etiologic mechanism involves the proliferation of residual embryologic parathyroid tissue that was not fully incorporated into the normal glands.[18] Clinically, parathyromatosis presents a formidable therapeutic challenge, as the numerous microscopic or miliary foci of hyperfunctioning tissue can sustain recurrent, persistent, or intractable hyperparathyroidism despite previous surgery.[19][20][21] While there are reports of partial biochemical control with calcimimetics, which enhance CaSR sensitivity, and with bisphosphonates, which inhibit bone resorption, these medical approaches rarely achieve complete or durable normalization of calcium and PTH levels.[19][21][22][23] Denosumab, a monoclonal antibody targeting the receptor activator of nuclear factor kappa-B ligand (RANKL), has been employed in some cases to provide longer-term management of hypercalcemia and skeletal complications.[18] Nevertheless, optimal treatment remains complete surgical excision of all hyperfunctioning nodules wherever feasible, although achieving this goal is often technically difficult due to the diffuse, scattered distribution of the parathyroid tissue.[19][21][22][23]

Normocalcemic primary hyperparathyroidism has emerged as a distinct clinical entity within the spectrum of primary hyperparathyroidism. It is defined by persistently elevated PTH levels over a period of at least six months in the setting of consistently normal corrected total calcium and ionized calcium

concentrations.[5][24] A critical prerequisite for this diagnosis is the exclusion of all causes of secondary hyperparathyroidism, including vitamin D deficiency, inadequate calcium intake or malabsorption, renal insufficiency, and certain medications.[5][24] Once secondary etiologies are ruled out, the persistently elevated PTH implies autonomous parathyroid overactivity despite normocalcemia. Imaging studies aimed at localizing hyperfunctioning glands, such as sestamibi scans or ultrasonography, are often less frequently positive in normocalcemic than in classical hypercalcemic primary hyperparathyroidism, likely reflecting milder or earlier disease.[5][24] Management principles are broadly similar to those for hypercalcemic primary hyperparathyroidism, focusing on careful biochemical and skeletal monitoring and consideration of surgery in selected patients with complications or disease progression.[5][24] Many individuals with normocalcemic primary hyperparathyroidism remain asymptomatic and do not require immediate intervention, instead undergoing routine follow-up to detect evolving skeletal, renal, or biochemical changes.[24] Lithium therapy is another important etiologic factor in hyperparathyroid states. Chronic lithium use can induce a functional resistance of the CaSR, thereby shifting the set-point at which serum calcium suppresses PTH secretion.[25][26][27] As a result, higher-than-normal calcium levels are required to adequately inhibit PTH release, predisposing to hypercalcemia. The true incidence of lithium-induced hyperparathyroidism is uncertain, as PTH levels are not routinely monitored in patients on long-term lithium therapy and many affected individuals remain asymptomatic.[25][26][27] Laboratory findings in lithium-related hyperparathyroidism typically include hypercalcemia, non-suppressed or elevated PTH, normal serum phosphorus, and hypocalciuria, a biochemical profile that can resemble familial hypocalciuric hypercalcemia.[25][26][27] Although considered a form of secondary hyperparathyroidism from a pathophysiological standpoint, lithium-associated disease can lead to parathyroid gland hypertrophy or adenoma formation and may present clinically in a manner similar to primary hyperparathyroidism, occasionally necessitating surgical intervention.[25][26][27]

Malignancy-related hypercalcemia represents a common and clinically serious cause of elevated serum calcium, occurring in approximately 20% to 30% of patients with cancer.[28][29] It can be easily mistaken for primary hyperparathyroidism, particularly when hypercalcemia constitutes the first overt manifestation of an otherwise occult malignancy.[28][29] The most frequent mechanism underlying malignancy-associated hypercalcemia is the production and secretion of PTH-related protein (PTHrP) by tumor cells, especially in squamous cell carcinomas of the lung and in renal cell carcinomas.[28][29] PTHrP binds to and activates the same receptor as PTH, thereby eliciting similar biological effects, including increased bone resorption, enhanced renal tubular calcium reabsorption, hypercalciuria, and hypophosphatemia.[28][29] However, the immunoassays used to measure PTH and PTHrP are distinct: PTH assays do not detect PTHrP, and PTHrP assays do not cross-react with PTH.[28][29][30] Consequently, patients with humoral hypercalcemia of malignancy typically exhibit markedly elevated PTHrP levels with suppressed or low PTH concentrations, a pattern that permits clear differentiation from primary hyperparathyroidism.[28][29][30] In patients without a known malignancy, the occurrence of hypercalcemia in conjunction with systemic or paraneoplastic-like features such as unexplained fatigue, weight loss, skin rashes, or muscle weakness should prompt a high index of suspicion for an underlying cancer.[30] Further details regarding this entity are provided in the companion StatPearls article on malignancy-related hypercalcemia.[28] A significant subset of primary hyperparathyroidism cases—up to 10%—has a hereditary basis, with various germline mutations predisposing to parathyroid overactivity.[10][31][32][33][34] Genetic syndromes associated with hyperparathyroidism include multiple endocrine neoplasia types 1, 2A, and 4; hyperparathyroidism–jaw tumor syndrome; familial isolated hyperparathyroidism; neonatal severe hyperparathyroidism; and familial hypocalciuric hypercalcemia.[10][31][32][33][34] A familial etiology should be considered particularly when primary hyperparathyroidism is diagnosed at an early age or when there is a family history of hypercalcemia, pituitary adenomas, pancreatic islet cell tumors, pheochromocytomas, or medullary thyroid carcinoma.[35] Recognition of such patterns has important implications not only for the affected individual but also for genetic counseling and screening of at-risk relatives.

Multiple endocrine neoplasias (MEN) are prototypical hereditary syndromes in which primary hyperparathyroidism is a key feature.[36] MEN syndromes characteristically involve multiple endocrine organs and often present with multiglandular parathyroid disease rather than solitary adenomas.[36] In MEN type 1, primary hyperparathyroidism is usually the earliest and most common clinical manifestation, often appearing between the ages of 20 and 25 years and ultimately occurring in more than 90% of affected individuals.[36] The parathyroid involvement in MEN type 1 is typically multiglandular, with diffuse hyperplasia of all parathyroid glands, and is frequently asymptomatic or mildly symptomatic in the early stages.[36] Surgical management is generally recommended when patients develop

symptoms, significant hypercalcemia, or end-organ complications, although the extent of parathyroid resection must be carefully tailored to balance the risks of persistent disease and hypoparathyroidism.[6] Further details on MEN types 1, 2, and 4 are provided in companion StatPearls references.[37][38][39] Tumor-jaw syndrome, also known as hyperparathyroidism–jaw tumor syndrome, is a rare autosomal dominant condition associated with primary hyperparathyroidism and a high risk of parathyroid carcinoma.[6] It is caused by mutations in the CDC73 gene, which encodes parafibromin, a tumor suppressor protein.[6] In addition to parathyroid adenomas and carcinomas, affected individuals often develop ossifying fibromas of the jaw and may also exhibit uterine tumors and renal abnormalities, including Wilms tumor and renal adenocarcinoma.[40] Because of the strong association with parathyroid malignancy, early recognition and vigilant surveillance are crucial in this syndrome.[6][40] Familial hypocalciuric hypercalcemia (FHH) is an autosomal dominant inherited disorder that can present with elevated PTH levels and chronic mild hypercalcemia.[41] It is most commonly caused by inactivating mutations in the CaSR on parathyroid chief cells, which reduce receptor sensitivity to serum calcium and thus shift the set-point for PTH suppression.[41] As a consequence, affected individuals exhibit mild hypercalcemia, hypophosphatemia, hypercalciuria as described in this context, and mildly elevated or inappropriately normal PTH concentrations.[41] In approximately 80% of cases, PTH levels are within the normal reference range but are inappropriate for the degree of hypercalcemia and hypophosphatemia, whereas in the remaining 20%, PTH levels are frankly elevated.[42] Histologically, the parathyroid glands appear normal in FHH, distinguishing it from primary hyperparathyroidism due to adenoma or hyperplasia.[42] A positive family history of hypercalcemia is usually present, and FHH is more likely when hypercalcemia is identified before the age of 40.[42] The condition is typically asymptomatic and does not require treatment, but correct diagnosis is essential to avoid unnecessary parathyroid surgery. Additional information is available in the companion StatPearls article on familial hypocalciuric hypercalcemia.[42][43]

Severe neonatal hyperparathyroidism represents a life-threatening manifestation of disordered CaSR function and is sometimes observed in offspring of parents with FHH who carry heterozygous CaSR mutations.[18] In neonates who inherit biallelic or more deleterious mutations, the resulting impairment of calcium sensing leads to profound, often extreme hypercalcemia shortly after birth.[18] Clinically, affected infants present with respiratory distress, skeletal abnormalities including rib cage deformities, muscular hypotonia, and failure to thrive.[18] Although some patients may initially exhibit partial responses to intensive medical management aimed at lowering serum calcium and stabilizing cardiorespiratory function, definitive treatment most often requires parathyroidectomy, which may need to be performed on an emergent basis to prevent fatal complications.[18] Familial isolated hyperparathyroidism encompasses a heterogeneous group of inherited disorders in which primary hyperparathyroidism occurs in the absence of other syndromic features.[18] This phenotype can result from various genetic mechanisms, including incomplete expression or penetrance of MEN1 or CDC73 mutations, pathogenic variants in CASR, or germline-activating mutations in the transcription factor GCM2.[18] Clinical manifestations are variable, ranging from mild asymptomatic hypercalcemia to more severe disease with complications analogous to sporadic primary hyperparathyroidism. Because familial isolated hyperparathyroidism may represent an incomplete form of a broader hereditary syndrome, careful evaluation and follow-up are required to detect additional endocrine or neoplastic manifestations over time.[18] Collectively, these diverse etiologies—ranging from sporadic adenomas and carcinomas to surgically induced parathyromatosis, medication-related effects, malignancy-associated humoral syndromes, and a variety of genetic conditions—highlight the complex pathobiology underlying hyperparathyroidism. A nuanced understanding of these causes, integrated with knowledge of normal parathyroid physiology, is fundamental for accurate diagnosis, rational selection of therapeutic strategies, and effective long-term management of patients with PTH-mediated disorders of calcium metabolism. [40][41][42][43]

Epidemiology

Primary hyperparathyroidism represents the leading identifiable cause of hypercalcemia in clinical practice, particularly among postmenopausal women.[44] It is notably more prevalent in females, with a reported female-to-male ratio of approximately 3:1 to 4:1, and it most commonly manifests in individuals between 50 and 60 years of age.[44] This pronounced sex and age predominance is often attributed to hormonal and metabolic changes associated with menopause, superimposed on age-related alterations in calcium and bone metabolism. The disorder has gradually transitioned from being regarded as a rare, overtly symptomatic endocrine disease to one that is frequently detected in its subclinical or mildly symptomatic form, largely due to evolving diagnostic practices and wider biochemical screening. A range of risk factors has been implicated in the development of primary hyperparathyroidism and related hypercalcemic states, reflecting a complex interplay between genetic predisposition, environmental influences, and medical therapies. Specific germline and somatic

mutations play a crucial pathogenic role, especially in familial and syndromic forms of the disease, where inherited defects in genes regulating parathyroid growth, differentiation, or calcium sensing can precipitate early-onset or multiglandular involvement.[45][46] In addition to these genetic determinants, several modifiable lifestyle and clinical factors have been associated with an increased risk of hyperparathyroidism. Chronically low dietary calcium intake can lead to prolonged stimulation of PTH secretion as the body attempts to maintain normocalcemia, potentially contributing over time to parathyroid hyperplasia and autonomous hormone production.[45] Obesity is another recognized risk factor, possibly mediated through chronic low-grade inflammation, altered vitamin D metabolism, and changes in adipokine profiles that affect bone and mineral metabolism.[46][47] Long-term use of loop diuretics such as furosemide has been linked to hyperparathyroidism as well, owing to their capacity to increase renal calcium excretion, which may chronically stimulate PTH secretion to compensate for urinary calcium losses.[48] A history of neck irradiation is also relevant, as radiation exposure can induce mutagenic changes and promote neoplastic transformation in parathyroid tissue.[49] Furthermore, lithium therapy, commonly used in the management of bipolar disorder, is known to alter the set-point of the calcium-sensing receptor, leading to higher serum calcium levels being required to suppress PTH secretion, thereby predisposing to hypercalcemia and hyperparathyroidism.[50] Additional associations have been observed with hypertension and physical inactivity, which may reflect broader cardiometabolic and lifestyle-related influences on mineral metabolism and endocrine function.[45][46][47][48][49][50]

Historically, thiazide diuretics were considered a potential risk factor for hyperparathyroidism and hypercalcemia because of their capacity to reduce urinary calcium excretion, thereby modestly raising serum calcium levels. However, more recent reviews suggest that thiazides are more likely to reveal or “unmask” an underlying parathyroid disorder rather than directly cause it.[51] In practice, when hypercalcemia is discovered in a patient taking thiazide diuretics, it is now recommended to discontinue the medication and reassess serum calcium levels after an appropriate interval. Persistence of hypercalcemia despite withdrawal of thiazide therapy is more consistent with an underlying diagnosis of primary hyperparathyroidism than with a purely drug-induced phenomenon.[51] The epidemiologic profile of primary hyperparathyroidism has changed substantially over the past several decades, largely due to the widespread availability of routine biochemical testing. Before approximately 1970, the disorder was most often diagnosed in patients who presented with classic and advanced symptoms, including recurrent nephrolithiasis, bone pain, pathological fractures, or overt skeletal deformities.[10] These clinical manifestations reflected longstanding and severe hypercalcemia, with significant involvement of the renal and skeletal systems. The introduction and increasing routine use of automated serum chemistry panels fundamentally altered this landscape. Serum calcium measurements became an integral component of standard laboratory evaluation, whether for general health screening, preoperative assessment, or investigation of unrelated complaints. As a result, primary hyperparathyroidism began to be detected far more frequently at earlier and less symptomatic stages, with asymptomatic or mildly symptomatic hypercalcemia serving as the most common initial clue to the diagnosis.[10] In many contemporary healthcare settings, particularly in high-income countries, the majority of cases are now identified through incidental findings of elevated calcium levels during routine testing rather than through the dramatic clinical presentations that once predominated. However, this epidemiologic shift is not uniform across all regions of the world. In countries or areas where vitamin D deficiency is widespread and routine biochemical screening is not consistently integrated into healthcare systems, the presentation of primary hyperparathyroidism often remains more symptomatic and advanced.[44][52][53] In such settings, patients are more likely to come to medical attention with pronounced skeletal manifestations, such as osteitis fibrosa cystica, bone pain, fractures, or significant loss of bone mass, as well as nephrolithiasis and associated renal complications.[44][52][53] Vitamin D deficiency, by contributing to secondary hyperparathyroidism and masking overt hypercalcemia, may also delay the recognition of primary hyperparathyroidism, thereby allowing more severe end-organ damage to develop before diagnosis. Consequently, the global epidemiology of primary hyperparathyroidism reflects not only intrinsic disease biology but also regional variations in nutrition, public health infrastructure, and access to laboratory testing.

In the United States, contemporary estimates suggest that the incidence of hyperparathyroidism is approximately 233 per 100,000 person-years in women and 85 per 100,000 person-years in men, underscoring the strong female predominance in diagnosis.[10] These figures also highlight that primary hyperparathyroidism is far from a rare condition in the adult population, particularly among older women. Moreover, racial and ethnic differences in incidence have been observed, especially in North American populations. Incidence appears to be higher among Black individuals compared with White individuals, while Asians and Hispanics tend to have lower incidence rates.[10] The reasons for these

disparities are likely multifactorial and may involve genetic susceptibility, environmental exposures, dietary patterns, variations in vitamin D status, differences in healthcare access, and patterns of laboratory testing. Such epidemiologic differences emphasize the importance of considering demographic context, social determinants of health, and potential disparities in screening and diagnostic practices when interpreting data on the burden of primary hyperparathyroidism. Parathyroid carcinoma, a malignant cause of primary hyperparathyroidism, is exceptionally rare, constituting less than 0.5% of all primary hyperparathyroidism cases.[54] Despite its rarity, it is epidemiologically significant because of its association with more severe biochemical and clinical manifestations. Patients with parathyroid carcinoma typically exhibit substantially higher serum calcium and PTH levels than those seen in benign primary hyperparathyroidism, often presenting with symptomatic, sometimes life-threatening hypercalcemia.[54] From an epidemiologic perspective, parathyroid carcinoma is also notable for its association with specific genetic syndromes, most prominently hyperparathyroidism–jaw tumor syndrome, an autosomal dominant disorder in which up to 15% of affected individuals develop parathyroid carcinoma.[55] This syndrome is further associated with a range of renal abnormalities, including Wilms tumors, hamartomas, and polycystic kidney disease, reflecting a broader systemic predisposition to neoplastic and cystic lesions.[56] Although the absolute number of cases remains small, awareness of these syndromic associations is important for risk stratification, early diagnosis, and surveillance among individuals with relevant family histories or genetic findings. Taken together, the epidemiology of primary hyperparathyroidism illustrates the dynamic interaction between advances in medical technology, regional patterns of nutrition and healthcare access, and underlying genetic and environmental risk factors. In high-resource settings with routine biochemical screening, the disease is now predominantly detected in its asymptomatic or mildly symptomatic stages, particularly among postmenopausal women, whereas in resource-limited environments and populations with widespread vitamin D deficiency, more advanced and symptomatic presentations remain common.[10][44][52][53] Recognition of established risk factors—including genetic predisposition, low dietary calcium intake, obesity, certain medications such as lithium and furosemide, prior neck irradiation, hypertension, and sedentary lifestyle—enables more informed clinical suspicion and targeted evaluation in at-risk individuals.[45][46][47][48][49][50] Furthermore, understanding the rarity yet clinical impact of parathyroid carcinoma, as well as its association with hereditary syndromes such as hyperparathyroidism–jaw tumor syndrome, offers important insights for oncologic and genetic risk assessment.[54][55][56] As diagnostic practices and population demographics continue to evolve, ongoing epidemiologic surveillance will remain essential to refine our understanding of disease patterns, inform screening strategies, and optimize the clinical management of patients with primary hyperparathyroidism.

Pathophysiology

Parathyroid hormone (PTH) is the principal endocrine regulator of calcium homeostasis and exerts its effects through coordinated actions on bone, kidney, and the gastrointestinal tract. Its overall physiological role is to increase and stabilize serum calcium concentrations within a narrow range, thereby ensuring proper neuromuscular function, coagulation, and intracellular signaling.[11] To achieve this, PTH modulates three major processes: skeletal mineral mobilization, renal tubular handling of calcium and phosphate, and the metabolism of vitamin D. In bone, PTH enhances resorptive activity, leading to the release of both calcium and phosphorus from the mineralized matrix into the circulation. This occurs through complex interactions with osteoblasts and osteoclasts, ultimately favoring osteoclastic bone resorption when PTH exposure is sustained. In the kidneys, PTH reduces urinary calcium excretion by increasing calcium reabsorption in the distal convoluted tubule and the thick ascending limb of the loop of Henle, thereby conserving calcium in the face of potential losses. Simultaneously, PTH stimulates the enzyme 1-α-hydroxylase in the proximal tubules, which converts 25-hydroxyvitamin D (25-VitD), a relatively inactive precursor, into the biologically active form, 1,25-dihydroxyvitamin D (1,25-VitD). This active metabolite then enhances intestinal absorption of both calcium and phosphorus, further contributing to the maintenance of adequate serum calcium levels.[11] Collectively, these actions result in a net increase in circulating calcium. In contrast, calcitonin, secreted by the parafollicular (C) cells of the thyroid gland, exerts a generally opposing effect by suppressing bone resorption and promoting calcium deposition into bone.[57] However, the physiological role of calcitonin in human calcium and bone metabolism appears limited, and it is not considered a major determinant of routine calcium homeostasis in adults.[57] The dominant antagonistic forces acting on calcium balance are therefore mediated through the interplay between PTH and vitamin D, with calcitonin serving more as a modulatory hormone with a relatively minor role in everyday regulation. PTH also exerts important effects on phosphate metabolism. It inhibits proximal tubular phosphate reabsorption in the kidney, leading to increased urinary phosphate excretion (phosphaturia). At the same time, the hormone enhances bone resorption and, via its stimulation of 1,25-VitD, increases gastrointestinal uptake of phosphorus.[11] The net result of these opposing

influences is that many patients with primary hyperparathyroidism exhibit serum phosphorus values that remain within the normal range, despite increased phosphate fluxes. Nonetheless, when hypercalcemia is accompanied by hypophosphatemia, this biochemical pattern is highly suggestive of hyperparathyroidism and can be diagnostically informative.[58][59]

Urinary calcium excretion in primary hyperparathyroidism is shaped by several interacting factors, including the degree of hypercalcemia, the glomerular filtration rate (GFR), and the tubular effects of PTH on calcium reabsorption. Under physiological conditions, PTH reduces urinary calcium excretion by enhancing distal tubular reabsorption. However, in the setting of significant hypercalcemia, the filtered load of calcium at the glomerulus can become so high that it exceeds the reabsorptive capacity of the nephron, leading to hypercalciuria despite elevated PTH.[10] For this reason, 24-hour urinary calcium excretion in patients with primary hyperparathyroidism is variable but is often increased, reflecting both increased filtered calcium and the limitations of tubular reabsorptive mechanisms in the face of sustained hypercalcemia. The calcium-sensing receptor (CaSR), which is central to the regulation of PTH secretion in the parathyroid glands, is also expressed in renal tubular cells, particularly in the thick ascending limb of the loop of Henle, where approximately 25% of filtered calcium is normally reabsorbed.[10] Loss-of-function defects in CaSR reduce the kidney's sensitivity to extracellular calcium and result in decreased urinary calcium excretion (hypocalciuria), as well as impaired urinary concentrating ability. Conversely, activating mutations of CaSR increase the receptor's responsiveness to calcium and promote enhanced urinary calcium losses (hypercalciuria).[10] These genetic variations in CaSR function illustrate the tight coupling between systemic calcium homeostasis, parathyroid function, and renal calcium handling. Under normal physiological conditions, extracellular calcium concentrations are maintained within a very narrow range through a network of hormonal regulatory mechanisms involving PTH, vitamin D metabolites, and, to a lesser extent, calcitonin.[11][60] Calcium enters the body primarily through the gastrointestinal tract, where it is absorbed via both passive diffusion and active, transcellular transport. The active transport component is strongly upregulated by 1,25-VitD, which increases the expression of calcium transport proteins in enterocytes, thereby enhancing intestinal calcium absorption.[11][60] PTH secretion itself is tightly regulated by serum calcium levels in a sigmoidal manner: physiologic PTH release is minimal when serum calcium is above approximately 10 mg/dL and reaches maximal secretion as calcium levels fall below about 7.5 mg/dL.[61] This steep response curve allows for rapid hormonal adjustment to even slight deviations in calcium concentration.

In the circulation, calcium exists in three principal forms. Roughly 50% of total serum calcium is bound to proteins, predominantly albumin. Approximately 45% is present as free, ionized calcium, which is the biologically active fraction responsible for most physiological effects. The remaining small fraction is complexed with anions such as phosphate and citrate. Because most clinical laboratories routinely report total serum calcium rather than ionized calcium, interpretation of calcium values must take serum albumin into account. A commonly used formula to estimate the albumin-corrected calcium is:

Corrected calcium = Measured calcium + 0.8 × (4.0 − albumin)

This calculation adjusts the total calcium concentration to a standardized albumin level of 4.0 g/dL, providing a better approximation of the physiologically relevant calcium status. However, caution is required when evaluating total calcium values in patients with hypoalbuminemia. In such individuals, total serum calcium may appear normal or even low, while the ionized calcium fraction may actually be elevated, indicating true hypercalcemia. Conversely, in some cases of low total calcium due to hypoalbuminemia, the ionized calcium may be normal, meaning that the patient is not truly hypocalcemic. Direct measurement of ionized calcium is therefore particularly useful in patients with significant alterations in serum protein levels. Chronic kidney disease (CKD) provides a classic example of how disturbances in vitamin D metabolism and renal function can alter PTH dynamics and lead to secondary and tertiary hyperparathyroidism. In CKD, declining renal function impairs the ability of the kidneys to generate adequate 1,25-VitD, resulting in diminished intestinal calcium absorption and a tendency toward hypocalcemia.[62][63][64][65] The fall in serum calcium, in turn, stimulates increased PTH synthesis and secretion as a compensatory response. Additionally, some PTH assays may give spuriously elevated readings in patients with renal failure, complicating interpretation of hormone levels.[66][67] Beyond impaired 1,25-VitD production, reduced clearance of PTH by the failing kidneys further contributes to elevated circulating PTH concentrations.[68][69] Persistent hypocalcemia and hyperphosphatemia, common in CKD due to decreased phosphate excretion, provide ongoing stimuli for parathyroid hyperactivity. Over time, this chronic stimulation leads to diffuse hyperplasia of all parathyroid glands, a hallmark of secondary hyperparathyroidism in the context of renal disease.[69][70][71]

Most patients with CKD initially develop secondary hyperparathyroidism, characterized

biochemically by elevated PTH levels with normal or low serum calcium. However, in some individuals, prolonged parathyroid hyperplasia progresses to a state of relative autonomy in which the glands continue to secrete excessive PTH even after correction of the original stimuli, such as improved calcium and phosphate balance with dialysis or transplantation. This condition is termed tertiary hyperparathyroidism and is distinguished by autonomous PTH overproduction and resulting hypercalcemia.[69][70][71] The evolution from secondary to tertiary hyperparathyroidism underscores how chronic perturbations in calcium–phosphate–vitamin D homeostasis can structurally and functionally remodel the parathyroid glands. In such cases, medical therapy may become insufficient, and parathyroidectomy is often required to restore more normal calcium and PTH levels. Further discussion of these processes, especially in relation to skeletal consequences such as renal osteodystrophy, is provided in the companion StatPearls article on that topic.[72] Taken together, the pathophysiology of primary and secondary hyperparathyroid states reflects an intricate balance between PTH secretion, target organ responsiveness, vitamin D metabolism, and renal function. Disruption at any point in this system—whether through autonomous glandular overactivity, receptor defects, reduced vitamin D activation, or impaired renal clearance—can destabilize calcium homeostasis and culminate in clinically significant hypercalcemia or, less commonly, hypocalcemia. A detailed understanding of these mechanisms is central to the accurate diagnosis, differentiation, and management of hyperparathyroid disorders in clinical practice [66][67][68][69][70][71][72].

Histopathology

The histopathological features of primary hyperparathyroidism reflect both the intrinsic characteristics of parathyroid lesions and the systemic skeletal consequences of prolonged PTH excess. Parathyroid adenomas, which account for the overwhelming majority of primary hyperparathyroidism cases, are typically solitary, encapsulated lesions composed predominantly of chief cells.[73] These chief cells resemble their normal counterparts but are arranged in a more compact, monotonous fashion and often demonstrate reduced interspersed adipose tissue, a histological hallmark distinguishing adenomatous glands from normal parathyroid tissue. The cellularity of adenomas is generally high, and the architectural organization may include solid, trabecular, or acinar patterns. Although chief cells represent the primary cell type involved, variations can occur. Oxyphil cell adenomas, though notably uncommon, have been described in a minority of patients.[73] These rare tumors are composed mainly of larger oxyphil cells with abundant eosinophilic, granular cytoplasm rich in mitochondria. Their functional significance remains incompletely understood, but their presence demonstrates the diversity of cellular phenotypes that can give rise to hyperfunctioning parathyroid tissue. Beyond the parathyroid glands themselves, the chronic biochemical derangements associated with sustained PTH elevation produce characteristic and sometimes severe changes in bone histology. Excessive PTH stimulates osteoclastic bone resorption by promoting osteoblast-mediated activation of osteoclast precursors. This results in increased osteoclastic number, size, and activity, ultimately leading to thinning of cortical bone, widening of Haversian canals, and increased trabecular bone porosity. Over time, if hyperparathyroidism remains untreated or unrecognized, these resorptive processes may become extensive enough to cause structural weakening and deformity of the skeleton.

One of the most distinctive skeletal manifestations is osteitis fibrosa cystica, a hallmark of advanced or long-standing hyperparathyroidism. This condition represents an exaggerated form of high-turnover bone disease in which the balance between bone formation and bone resorption is profoundly disrupted. Histologically, osteitis fibrosa cystica is defined by numerous and activated osteoclasts eroding trabecular and cortical bone, accompanied by the replacement of normal bone architecture with fibrovascular stromal tissue.[74] Areas of resorption often become filled with granulation tissue, and the accumulation of hemosiderin-laden macrophages within these lesions imparts a characteristic brown coloration. These hemosiderin-rich zones form what are termed “brown tumors,” which, despite their name, are not true neoplasms but rather represent reparative granulomatous responses to chronic bone resorption.[74] Brown tumors may occur in various skeletal sites—including the ribs, pelvis, clavicles, and long bones—and can mimic lytic bone lesions on imaging studies, occasionally raising concern for metastatic disease or primary bone malignancies. Histologically, they consist of fibroblastic proliferation, multinucleated giant cells resembling osteoclasts, hemorrhage, and hemosiderin deposition, all reflecting the cyclical processes of bone destruction and attempted repair. In addition to osteitis fibrosa cystica, prolonged PTH excess contributes to subperiosteal resorption, particularly evident along the radial aspects of the middle phalanges, and can lead to trabecular thinning, cortical tunneling, and eventual skeletal fragility. These changes reflect the pervasive impact of hyperparathyroidism on bone remodeling dynamics. Although such dramatic skeletal abnormalities are now less commonly encountered in clinical practice due to earlier detection of primary hyperparathyroidism, they remain an important histopathologic correlate of the disease in untreated or severe cases. Taken together, the histopathology of

primary hyperparathyroidism encompasses both the microscopic morphology of parathyroid tumors—most often chief cell adenomas—and the profound alterations in bone architecture resulting from chronic PTH excess. These changes underscore the systemic reach of parathyroid pathology and the importance of timely diagnosis and management to prevent irreversible skeletal damage.[73][74]

History and Physical

Clinical Features

Historically, the typical presentation of primary hyperparathyroidism was overt and often striking. In earlier decades, most patients came to medical attention because of symptomatic complications such as recurrent nephrolithiasis, persistent bone pain, fragility fractures, proximal muscle weakness, and, in advanced cases, skeletal deformities.[75] With the advent and widespread use of automated biochemical screening in the 1970s, the clinical landscape changed significantly. In contemporary practice, particularly in developed countries, the majority of patients with primary hyperparathyroidism are identified while still asymptomatic, after an elevated serum calcium concentration is incidentally detected on a routine chemistry panel obtained for screening or for evaluation of unrelated complaints.[75] A definitive diagnosis is then established through targeted laboratory evaluation, typically demonstrating inappropriately elevated or non-suppressed parathyroid hormone (PTH) levels in the setting of hypercalcemia. A thorough clinical history remains essential despite the frequent asymptomatic nature of the disease at diagnosis. Clinicians should systematically inquire about any prior episodes of kidney stones or renal colic, as these may reflect previously unrecognized hypercalciuria and nephrolithiasis related to hyperparathyroidism.[44] Questions should also address bone pain, a history of low-impact or pathological fractures, and generalized myalgias or muscle weakness, as these may signal skeletal involvement or neuromuscular effects of chronic hypercalcemia. Because primary hyperparathyroidism can also manifest with neuropsychiatric and constitutional symptoms, patients should be asked about depressed mood, irritability, memory difficulties, poor concentration, or changes in sleep patterns, as well as nonspecific fatigue or decreased exercise tolerance.[44] Medication and supplement histories are particularly important. Clinicians should specifically review the use of thiazide diuretics, calcium-containing antacids or supplements, and vitamin D preparations, as these can alter calcium homeostasis and either exacerbate or unmask underlying parathyroid disease.[44] The use of lithium, which can modify the set-point of the calcium-sensing receptor, should also be explored, as it may contribute to hypercalcemia and complicate the interpretation of PTH levels. In addition, it is valuable to consider other potential causes or contributors to hypercalcemia, such as malignancy, granulomatous disease, or prolonged immobilization, to ensure an appropriately broad differential diagnosis.

Although many patients report no symptoms at the time hypercalcemia is first noted, more detailed evaluation often reveals subclinical or previously unrecognized complications. Imaging studies have demonstrated that up to 55% of individuals with primary hyperparathyroidism harbor nephrocalcinosis or nonobstructing renal calculi that had not previously been diagnosed.[76][77][78] Among those who are symptomatic, as many as three-quarters may present with acute renal colic or clinically obvious nephrolithiasis.[76][77][78] Given this strong association, measurement of serum calcium is recommended in all patients presenting with calcium-containing kidney stones, as primary hyperparathyroidism is an important and treatable cause of nephrolithiasis.[76][77][78] The likelihood of overt hypercalcemic symptoms tends to increase with the severity of the biochemical abnormality. When the serum calcium concentration exceeds approximately 12 mg/dL, patients are far more likely to experience classic hypercalcemic manifestations, including anorexia, nausea, constipation, dehydration, polyuria, polydipsia, and various degrees of cognitive or mental status changes.[79] In this context, neurocognitive complaints may range from subtle difficulties with attention and memory to confusion, lethargy, or, in extreme cases, stupor. Approximately 40% of patients with primary hyperparathyroidism have demonstrable hypercalciuria on 24-hour urine collection, reflecting both the increased filtered load of calcium and the limitations of tubular reabsorption in the face of sustained hypercalcemia.[80] Even after successful parathyroidectomy, the risk of recurrent nephrolithiasis does not immediately return to baseline. In patients with primary hyperparathyroidism and a history of kidney stones, the risk of future stone formation is reduced but may persist for 10 to 15 years following curative surgery.[81] This persistent risk underscores the importance of ongoing metabolic evaluation and risk-factor modification after parathyroidectomy. A 24-hour urine biochemical profile is therefore recommended for patients with nephrolithiasis, even after surgical cure, to identify and address other lithogenic abnormalities such as hyperoxaluria, hypocitraturia, or low urine volume that may contribute to stone formation.[82]

On physical examination, most individuals with primary hyperparathyroidism appear clinically well, and the examination is frequently unremarkable. Nevertheless, a careful and comprehensive assessment is crucial, both to identify possible complications and to search for alternative or coexisting causes of hypercalcemia. Parathyroid

adenomas are generally small and nonpalpable, so a normal neck examination does not exclude the diagnosis. However, the finding of a large, firm, or irregular neck mass in a patient with hypercalcemia should raise suspicion for parathyroid carcinoma, particularly when accompanied by markedly elevated PTH levels and severe hypercalcemia.[83] The physical examination may also reveal evidence of hypertension, volume depletion, or signs of chronic kidney disease, as well as skeletal tenderness or deformities in advanced or long-standing disease. Clinical manifestations associated with hyperparathyroidism and hypercalcemia extend beyond the renal and skeletal systems. Patients may report abdominal pain, which can arise from peptic disease, pancreatitis, or constipation. Cardiac involvement can manifest as arrhythmias, reduced coronary flow reserve, or left ventricular hypertrophy, contributing to an increased overall burden of cardiovascular disease. Musculoskeletal complaints are common and may include diffuse body aches, joint pain, and proximal muscle weakness. Neuropsychiatric and cognitive effects can be subtle but debilitating, encompassing depression, forgetfulness, difficulty concentrating, headaches, insomnia, and chronic fatigue. Many patients describe a vague sense of feeling unwell or "not themselves," with frequent complaints of illness that defy easy explanation. Osteoporosis and increased fracture risk may be documented by bone densitometry or by history of low-trauma fractures. Polyuria and nocturia may reflect both hypercalcemia-induced nephrogenic diabetes insipidus and underlying renal impairment. In some patients, aortic valve calcification and other vascular calcifications may be detected, indicative of the systemic nature of calcium-phosphate imbalance in chronic disease.

Acute primary hyperparathyroidism

Acute primary hyperparathyroidism, also referred to as parathyroid crisis or parathyroid storm, represents a rare but life-threatening endocrine emergency. It is characterized by an abrupt and severe exacerbation of hypercalcemia in a patient with known or previously unrecognized primary hyperparathyroidism.[84][85] Laboratory evaluation reveals markedly elevated serum calcium levels, typically exceeding 14 mg/dL, in conjunction with PTH concentrations that may rise to 20 times the upper limit of normal.[84][85] This clinical picture may occasionally be associated with underlying parathyroid carcinoma, although it can also occur in the setting of benign adenomas.[86] Extreme hypercalcemia, particularly when serum calcium exceeds 15 mg/dL, can rapidly become fatal if not promptly recognized and treated. Patients may develop profound dehydration, acute kidney injury, cardiac arrhythmias, encephalopathy, and progression to coma.[79] Management of parathyroid crisis centers on aggressive and timely reduction of serum calcium levels. Initial therapy typically includes vigorous intravenous hydration with normal saline to restore intravascular volume and enhance renal calcium excretion, followed by loop diuretics such as furosemide (but not thiazides) to promote calciuresis once volume status is adequate.[79][87][88][89][90][91] Calcitonin can be administered for its rapid, although transient, hypocalcemic effect. Intravenous bisphosphonates are used to inhibit osteoclastic bone resorption, but their maximal effect may take several days to manifest.[79][87][88][89][90][91] Denosumab, a monoclonal antibody targeting RANK-ligand, has also been utilized in severe hypercalcemia, and the 2023 Endocrine Society Clinical Practice Guidelines recommend its use, particularly in refractory cases.[92] While some evidence suggests that bisphosphonates may be more effective overall, denosumab is a reasonable consideration in patients who do not respond adequately to bisphosphonate therapy.[92] In patients with severe hypercalcemia unresponsive to pharmacologic measures, or in those with significant renal impairment, dialysis can be employed as a temporizing measure to remove excess calcium from the circulation.[93][94] This may be considered even in patients without established renal failure if other therapies have failed. Dialysate composition may require adjustment, particularly with respect to calcium and phosphate concentrations, to prevent complications such as hypophosphatemia.[94] Ultimately, definitive treatment of acute primary hyperparathyroidism requires surgical removal of the hyperfunctioning parathyroid tissue. Emergency or urgent parathyroidectomy, once the patient is hemodynamically stabilized and calcium levels are partially controlled, provides curative therapy and prevents recurrence of the crisis.[84][85][86][95]

Osteitis fibrosa cystica

Osteitis fibrosa cystica represents a late and severe osseous complication of long-standing, untreated, or poorly controlled hyperparathyroidism. Clinically, it is characterized by painful bony swelling, skeletal deformities, reduced bone mineral density, and an increased propensity to fractures.[96] Radiographic and histologic features include subperiosteal bone resorption, cortical thinning, trabecular rarefaction, and the formation of cyst-like lesions and brown tumors. Although once a classic manifestation of primary hyperparathyroidism, particularly in eras and regions where diagnosis was delayed, osteitis fibrosa cystica has become rare in the developed world due to earlier recognition of hyperparathyroidism through routine biochemical screening.[96] When it does occur, definitive treatment of the underlying parathyroid disorder—especially surgical parathyroidectomy—halts the excessive PTH drive and allows gradual healing and remodeling of bone. With appropriate therapy, symptoms typically improve, bone density increases,

and the risk of further fractures declines. Further details are available in the companion StatPearls article devoted specifically to osteitis fibrosa cystica.[96]

Evaluation

The systematic evaluation of a patient with hypercalcemia begins with determining whether the process is mediated by parathyroid hormone and, if so, whether primary hyperparathyroidism is the underlying cause. All individuals with elevated serum calcium levels should undergo biochemical assessment for hyperparathyroidism, as early recognition has important implications for renal, skeletal, and cardiovascular outcomes.[44] Although the concurrence of hypercalcemia with hypophosphatemia is highly suggestive of hyperparathyroidism or humoral hypercalcemia of malignancy, it is not in itself diagnostic. Most patients with primary hyperparathyroidism, particularly those identified by screening in developed healthcare settings, actually have phosphorus levels within the reference range. Nevertheless, when hypercalcemia is accompanied by hypophosphatemia, the combination is especially consistent with PTH-mediated disease or PTH-related protein–driven malignancy.[44][58][59] The cornerstone of diagnosis is the demonstration of hypercalcemia—either as elevated ionized calcium or appropriately albumin-corrected total calcium—in the presence of an inappropriately elevated parathyroid hormone concentration.[44] In physiological states, hypercalcemia suppresses PTH secretion; therefore, most non-parathyroid causes of hypercalcemia are characterized by low or undetectable PTH levels. In primary hyperparathyroidism and other PTH-dependent hypercalcemic conditions, PTH values are frequently frankly elevated above the upper limit of normal. In some individuals, however, PTH may fall within the laboratory reference range but is still considered “inappropriately normal” because it fails to suppress in the context of high serum calcium.[44] In contrast, PTH levels should be very low or undetectable in PTH-independent hypercalcemia, such as malignancy-associated hypercalcemia (excluding rare ectopic PTH secretion), vitamin D intoxication, or thyrotoxicosis. Interpretation of PTH must also account for physiological variations: PTH concentrations tend to increase with age, and in populations where vitamin D deficiency is prevalent, the upper limit of what is considered “normal” PTH may be higher because of chronic secondary hyperparathyroid stimulation.[97]

A careful assessment of vitamin D status is essential, as vitamin D deficiency independently stimulates PTH secretion and can confound the diagnosis. Borderline or low 25-hydroxyvitamin D levels should be corrected with appropriate supplementation to achieve values above 30 ng/mL, thereby minimizing the contribution of secondary hyperparathyroidism to elevated PTH concentrations.[4] After repletion, persistently elevated PTH in the setting of hypercalcemia provides stronger support for a diagnosis of primary hyperparathyroidism rather than vitamin D–driven secondary hyperparathyroidism. For PTH measurement, immunochemiluminometric or immunoradiometric intact PTH assays are recommended, as these methods reliably distinguish primary hyperparathyroidism from malignancy-associated hypercalcemia and do not detect PTH-related protein.[44] PTH-related protein, the mediator of humoral hypercalcemia of malignancy, is structurally distinct and is not measured by standard intact PTH assays. Attention must also be paid to factors that can artifactually alter assay results. Biotin (vitamin B7), increasingly used in high doses as a nutritional supplement, is known to interfere with several immunoassays, including those for PTH, leading to misleadingly high or low hormone levels.[98] In patients taking biotin, supplementation should be discontinued and PTH reassessed after an appropriate washout period to ensure accurate measurement.[98] Similarly, medications that influence calcium sensing and renal handling, such as lithium and thiazide diuretics, should be reviewed. Where feasible, such drugs should be discontinued for three to six months, and serum calcium and PTH levels repeated.[25][26][27][51] If hypercalcemia and elevated or inappropriately normal PTH persist despite stopping these agents, primary hyperparathyroidism becomes a far more likely diagnosis. A critical step in the diagnostic pathway is distinguishing primary hyperparathyroidism from familial hypocalciuric hypercalcemia (FHH), a benign genetic condition that can closely mimic primary hyperparathyroidism biochemically. This differentiation is most effectively achieved through 24-hour urine collections for calcium and creatinine, from which both absolute urinary calcium excretion and the calcium clearance ratio can be calculated.[41][42][99] In FHH, urinary calcium excretion is usually low, often below 100 mg per 24 hours, reflecting reduced renal calcium excretion due to loss-of-function mutations in the calcium-sensing receptor.[41][42][99] The calcium clearance ratio—calculated as (urinary calcium × serum creatinine) / (serum calcium × urinary creatinine)—is typically less than 0.01 in FHH.[99] In contrast, patients with primary hyperparathyroidism generally have higher urinary calcium excretion, and their calcium clearance ratio is usually greater than 0.02.[99] Results between 0.01 and 0.02 fall into a gray zone and may be influenced by vitamin D deficiency, low dietary calcium intake, or chronic kidney disease, all of which can lower urinary calcium. In such cases, repeating the test after vitamin D repletion and optimization of calcium intake is advisable to clarify the diagnosis.[99] Although infrequently performed,

a calcium infusion test can further differentiate these entities: administration of a calcium load increases urinary calcium excretion in primary hyperparathyroidism but not in FHH.[42][99]

Reviewing prior medical records can provide important longitudinal context. Many individuals with primary hyperparathyroidism have had intermittent or persistent mild hypercalcemia for years before a diagnosis is formally recognized.[10] Conditions other than hyperparathyroidism rarely allow a healthy-appearing person to remain hypercalcemic for extended periods without clear systemic manifestations, making a long history of asymptomatic or mildly symptomatic hypercalcemia highly suggestive of PTH-mediated disease. In patients with PTH-independent hypercalcemia or when the diagnosis remains uncertain, additional targeted studies may be warranted. These can include PTH-related protein levels (to investigate humoral hypercalcemia of malignancy), serum and urine protein electrophoresis (for suspected multiple myeloma or related disorders), 1,25-dihydroxyvitamin D levels (for granulomatous disease or lymphoma), thyroid function tests, or appropriate imaging such as mammography, depending on the overall clinical context.[28][29][30] A comprehensive laboratory evaluation of suspected primary hyperparathyroidism therefore typically includes measurement of intact PTH, total and ionized calcium, serum phosphorus, 25-hydroxyvitamin D, serum albumin (to calculate corrected calcium), serum creatinine and blood urea nitrogen (BUN) to assess renal function, and alkaline phosphatase as a non-specific marker of bone turnover.[4][10][60] Twenty-four-hour urine collections provide urinary calcium and creatinine, permitting not only the calcium clearance ratio but also an assessment of creatinine clearance and overall kidney function. Bone mineral density is evaluated by dual-energy X-ray absorptiometry (DEXA), ideally at the lumbar spine, total hip, femoral neck, and distal one-third radius. The distal radius is of particular interest because it is rich in cortical bone, which is preferentially affected by PTH excess; declines in bone density at this site are common in primary hyperparathyroidism and may precede more obvious skeletal events.[3] In patients diagnosed at a young age, those with multiglandular disease, or those with a family history suggestive of a hereditary endocrine syndrome, genetic testing should be considered to evaluate for conditions such as multiple endocrine neoplasia, hyperparathyroidism–jaw tumor syndrome, or familial isolated hyperparathyroidism.[35][100] Imaging studies play a crucial role in the preoperative evaluation of patients who are candidates for parathyroidectomy, but they are not required to establish the biochemical diagnosis of primary hyperparathyroidism. Because localization studies can yield false-negative or misleading results, particularly in multiglandular disease, they are best reserved for surgical planning rather than initial diagnostic confirmation.[101] Neck ultrasonography and technetium-99m sestamibi scintigraphy are the conventional first-line imaging modalities used to localize hyperfunctioning parathyroid tissue. Ultrasound is noninvasive, widely available, and free of ionizing radiation. Its diagnostic accuracy is highly operator dependent, with optimal results obtained in centers with substantial experience and expertise.[102] Ultrasonography can identify enlarged parathyroid glands and concomitant thyroid nodules, which may influence surgical strategy. Sestamibi scanning, especially when combined with single-photon emission computed tomography (SPECT), provides functional imaging based on differential radiotracer uptake and washout in parathyroid versus thyroid tissue.[103][104][105] However, sestamibi is less sensitive for small adenomas, particularly those weighing less than 500 mg, and may be less effective in multiglandular hyperplasia.[103][104]

When first-line localization with ultrasonography and sestamibi scanning is negative, discordant, or equivocal, more advanced imaging modalities may be employed. Four-dimensional computed tomography (4D CT), which incorporates multiphase contrast-enhanced imaging to evaluate both the anatomy and vascular perfusion characteristics of the neck and upper mediastinum, has emerged as a powerful tool in difficult cases.[105][106] Evidence suggests that 4D CT may be superior to sestamibi SPECT/CT in localizing parathyroid adenomas, particularly in patients with prior neck surgery, ectopic glands, or complex anatomy.[107] However, implementation of 4D CT requires specialized protocols, appropriate radiologic expertise, and careful consideration of radiation exposure.[106][108] More recently, F-18-fluorocholine positron emission tomography/computed tomography (PET/CT) has shown promise in localizing parathyroid adenomas, particularly in patients with negative or inconclusive conventional imaging. Early studies suggest that fluorocholine PET/CT may outperform sestamibi scanning, ultrasound, or standard CT alone in selected challenging cases.[109] Novel and adjunctive techniques are also being explored. Infrared thermal imaging, for example, relies on the observation that hyperfunctioning parathyroid lesions are hypervascular and slightly warmer—by approximately two degrees Celsius—than surrounding tissues.[110] Thermal scanning has successfully identified adenomas that were not easily visualized by other modalities and may provide complementary information in cases with conflicting imaging findings.[110] In rare circumstances where noninvasive imaging fails to localize abnormal glands, selective parathyroid venous sampling can be considered. This invasive procedure involves catheter-based sampling of venous blood from

different regions of the neck and mediastinum to identify gradients in PTH concentration that correspond to the anatomical location of hyperfunctioning tissue.[111][112] Although technically demanding and not routinely required, selective venous sampling can be valuable in re-operative cases or in patients with persistent or recurrent hyperparathyroidism when standard imaging has been inconclusive.

Assessment of skeletal involvement is a key component of the evaluation, as primary hyperparathyroidism exerts profound effects on bone turnover and microarchitecture. Bone biopsy is seldom necessary, as noninvasive imaging provides substantial information about bone quantity and quality. DEXA remains the standard technique for quantifying bone mineral density at clinically relevant sites, but newer imaging and analytic approaches have revealed that the impact of PTH excess on bone structure may be more extensive than suggested by bone density alone.[3][113] The trabecular bone score (TBS), derived from DEXA images, provides an indirect measure of trabecular microarchitecture by quantifying textural variations in the lumbar spine region.[113] In primary hyperparathyroidism, TBS often indicates decreased connectivity and deterioration of the trabecular network, even when the DEXA T-score at the spine is not significantly reduced.[113] This suggests that microarchitectural damage may precede or exceed changes detectable by standard bone density measurements. High-resolution peripheral quantitative CT (HR-pQCT) of the distal radius and tibia offers even more detailed three-dimensional insights into skeletal microstructure. Studies using HR-pQCT have demonstrated that patients with primary hyperparathyroidism exhibit fewer, thinner, and more widely spaced trabeculae, as well as cortical thinning and increased cortical porosity.[114][115][116] These microstructural changes likely contribute to the relatively high prevalence of vertebral fractures observed in primary hyperparathyroidism, even in individuals whose lumbar spine bone mineral density appears preserved by DEXA criteria.[117][118][119] Many vertebral fractures in this context may be clinically silent and detected only by vertebral fracture assessment or spine imaging, underscoring the importance of comprehensive skeletal evaluation.[120] Taken together, the evaluation of primary hyperparathyroidism is a multi-step process that integrates biochemical, clinical, imaging, and skeletal data. Initial laboratory testing establishes whether hypercalcemia is PTH-dependent and distinguishes primary hyperparathyroidism from secondary causes and from FHH. Careful review of medications, supplements, and prior laboratory values refines this assessment, while targeted investigations, such as PTH-related protein or advanced imaging, are tailored to the individual patient's presentation. Localization studies are reserved for patients in whom surgery is contemplated and function primarily as operative roadmaps rather than diagnostic tools. Advanced skeletal imaging and indices such as TBS or HR-pQCT reveal the often-subtle but clinically important effects of PTH excess on bone strength. A thorough and methodical evaluation not only confirms the diagnosis but also characterizes disease severity, identifies complications, and informs decisions regarding surgical versus conservative management [115][116][117][118][119][120].

Treatment / Management

In 2022, an international multidisciplinary task force comprising endocrinologists, nephrologists, pathologists, epidemiologists, radiologists, pharmacologists, and endocrine surgeons issued updated evidence-based guidelines for the management of primary hyperparathyroidism.[4][5][6][10][74] These recommendations emphasize an individualized approach that integrates biochemical severity, skeletal and renal involvement, age, comorbidities, and patient preference, while reaffirming that surgical intervention remains the only definitive curative therapy for this disorder. From a therapeutic standpoint, parathyroidectomy is regarded as the gold standard and definitive treatment for primary hyperparathyroidism. Nonetheless, nonoperative surveillance is a reasonable and often appropriate alternative for carefully selected individuals, particularly older patients with mild, stable hypercalcemia who lack significant renal, skeletal, or neurocognitive complications and for whom surgical or anesthetic risk is elevated.[4][5][6][10] In addition, targeted medical therapies such as bisphosphonates, denosumab, and cinacalcet can provide substantial benefit in controlling osteoporosis and hypercalcemia in patients who are not candidates for surgery or who decline operative treatment. The decision to recommend parathyroid surgery is therefore based on a composite assessment that includes chronological age, the degree and chronicity of hypercalcemia, the presence of renal stones or nephrocalcinosis, objective evidence of bone disease, and competing medical conditions that may increase operative risk. For patients in whom surgery is deferred or contraindicated, thoughtful medical management and structured surveillance are critical. Contrary to older practices, dietary calcium intake should not be routinely restricted, as inadequate calcium intake can further stimulate PTH secretion and worsen hyperparathyroid bone disease.[5] In fact, patients with concomitant osteoporosis may require calcium supplementation to support skeletal health. Vitamin D status plays a particularly important role: robust evidence indicates that chronic vitamin D deficiency is both a risk factor for developing primary hyperparathyroidism and a driver of secondary PTH

elevation in affected individuals.[122][123] Consequently, current expert consensus recommends that patients with primary hyperparathyroidism who are deficient in vitamin D should receive supplementation sufficient to achieve a 25-hydroxyvitamin D concentration above 30 ng/mL, while monitoring serum calcium to avoid exacerbating hypercalcemia.[4][5][124]

Longitudinal cohort studies following patients with untreated primary hyperparathyroidism for up to 15 years have provided important insights into the natural history of the disease under nonoperative surveillance.[44][125] In general, biochemical parameters such as serum calcium, phosphorus, and PTH remain relatively stable over time in many patients, suggesting that the disorder may follow a slowly progressive or even plateauing course in some cases. However, skeletal outcomes are less benign. A gradual decline in bone mineral density becomes apparent after approximately 8 to 9 years of follow-up, with more marked reductions emerging after the tenth year.[44][125] While most individuals experience modest loss, a subset lose more than 10% of their bone mineral density by 15 years.[125] Renal function, by contrast, tends to remain stable in many patients, although hypercalciuria usually persists and continues to confer an elevated risk of nephrolithiasis over time.[125] Given these long-term trends, contemporary guidelines outline a structured monitoring program for patients managed medically.[4]5 Annual laboratory evaluation should include serum calcium, 25-hydroxyvitamin D, and an assessment of renal function, typically via creatinine and estimated creatinine clearance. PTH concentrations may be rechecked periodically or when clinically indicated, such as when hypercalcemia worsens or symptoms evolve. Repeat 24-hour urine calcium measurements, abdominal imaging to detect nephrolithiasis or nephrocalcinosis, and vertebral radiographs may be performed when new symptoms arise or when there is concern for progression. Bone mineral density should be assessed with three-site DEXA scanning—spine, hip, and distal one-third radius—at annual or biannual intervals to identify significant skeletal deterioration that might prompt reconsideration of surgical treatment.[4] Medical therapy in primary hyperparathyroidism is targeted primarily at two key objectives: amelioration of osteoporosis and control of hypercalcemia. Cinacalcet, a calcimimetic agent, effectively lowers serum calcium but generally does not improve bone mineral density, whereas antiresorptive agents such as bisphosphonates and denosumab increase bone density but are less effective at normalizing serum calcium.[5][121][126][127] In patients who have both significant hypercalcemia and low bone mass, a combination of cinacalcet and an antiresorptive agent can therefore be considered to address both aspects of the disease simultaneously.[5][121][126][127]

Oral bisphosphonates and the monoclonal antibody denosumab are the principal antiresorptive medications used to treat hyperparathyroid-associated osteoporosis or osteopenia.[44][121][128][129] These agents reduce bone turnover, increase bone mineral density, and have been shown to improve skeletal strength in patients with primary hyperparathyroidism. Denosumab, in particular, has been reported to control refractory hypercalcemia in some cases, while intravenous bisphosphonates can lower serum calcium rapidly and are valuable in the acute management of severe hypercalcemia.[130][131][132][133] However, intravenous bisphosphonates are not considered practical or safe for long-term, chronic therapy because of potential adverse effects such as osteonecrosis of the jaw and atypical femoral fractures, as well as the challenges of repeated parenteral administration.[130][131][132][133] Medications that directly activate the calcium-sensing receptor, most notably cinacalcet, represent a cornerstone of pharmacologic treatment for PTH-dependent hypercalcemia.[134][135] By increasing the sensitivity of the CaSR to extracellular calcium, cinacalcet suppresses PTH secretion and lowers serum calcium. Clinical trials and post-marketing studies suggest that more than 70% of patients treated with cinacalcet achieve normalization of serum calcium.[134][135][136][137] PTH levels typically decrease by approximately 35% to 50%, although they may not always fall into the reference range even when calcium is normalized.[138][139] Cinacalcet is especially valuable for patients with otherwise intractable hyperparathyroidism, including those with inoperable parathyroid carcinoma, in whom it can normalize or substantially reduce serum calcium levels and mitigate hypercalcemic symptoms.[138][140] Vitamin D status and urinary calcium excretion are generally not markedly altered by cinacalcet therapy.[138][139][140] In addition to its role in primary disease, cinacalcet is widely used for secondary hyperparathyroidism in chronic kidney disease.[141] Estrogen therapy has been evaluated in postmenopausal women with primary hyperparathyroidism and has demonstrated improvements in bone mineral density, particularly at the lumbar spine, without significant changes in serum calcium or PTH levels.[142][143][144] However, concerns regarding the risks associated with long-term estrogen use, including thromboembolic events, breast cancer, and cardiovascular complications, have limited its routine application in this context. As a result, estrogen is not generally recommended as first-line medical therapy for primary hyperparathyroidism, although it may be considered in selected cases where menopausal symptoms and bone loss coexist and alternative options are unsuitable.[142]

Oral phosphate therapy, once more commonly used, can lower serum calcium by up to approximately 1 mg/dL through its ability to bind dietary calcium in the gut, reduce intestinal calcium absorption, lower active vitamin D levels, and diminish bone resorption.[145][146] However, phosphate supplementation can paradoxically increase PTH secretion and promote soft tissue or vascular calcification, particularly when calcium-phosphate product becomes elevated. Consequently, oral phosphates are no longer recommended as routine long-term therapy in primary hyperparathyroidism and are used only in very selected circumstances.[145][146] Despite advances in medical therapy, surgical parathyroidectomy remains the treatment of choice for patients with symptomatic disease, particularly those with recurrent nephrolithiasis, nephrocalcinosis, or overt skeletal pathology such as osteoporosis, fractures, or osteitis fibrosa cystica.[4][147][148] Successful parathyroidectomy results in permanent normalization of serum calcium and a substantial reduction in PTH levels, with robust and sustained improvements in bone mineral density and quality at multiple skeletal sites.[114][149][150][151][152][153] Following surgery, cortical and trabecular bone architecture and strength improve, vertebral and nonvertebral fracture risk declines, and the frequency of kidney stone events diminishes.[114][149][150][151][152][153] Long-term follow-up data from Rubin and colleagues demonstrate that bone mineral density can increase by around 10% at all measured sites after curative parathyroidectomy, with these benefits sustained for at least 15 years.[125][154] Importantly, these skeletal advantages accrue even in patients who did not meet classical guideline criteria for surgery at the time of their operation.[125][154] The impact of surgery on neurocognitive function and cardiovascular risk is less clear. Some reports indicate that patients with cognitive impairment, mood disturbances, or nonspecific fatigue may experience rapid improvement in mental functioning within weeks of parathyroidectomy.[155][156][157][158] However, controlled data are inconsistent, and the Fifth International Workshop task force concluded that evidence is currently insufficient to formally recommend parathyroidectomy solely to improve quality of life, neurocognitive outcomes, or cardiovascular parameters.[4]

Surgery remains an option for essentially all patients with primary hyperparathyroidism, provided there are no major contraindications and both patient and clinician agree on the treatment goals. Optimal outcomes are achieved when operations are performed by experienced endocrine surgeons who regularly undertake parathyroid procedures and are proficient in the interpretation of preoperative localization studies.[6][159][160] In such hands, cure rates exceed 95%.[6][159][160] Current international guidelines endorse surgery as the preferred treatment for all symptomatic patients.[4] For asymptomatic individuals, parathyroidectomy is recommended when one or more of the following criteria are met: age younger than 50 years; creatinine clearance or glomerular filtration rate below 60 mL/min; radiographic evidence of renal stones, nephrolithiasis, or nephrocalcinosis; hypercalciuria exceeding 300 mg per 24 hours in men or 250 mg per 24 hours in women; osteoporosis with a T-score below −2.5 at any skeletal site; serum calcium consistently more than 1 mg/dL above the upper limit of normal; or the presence of a vertebral compression fracture on imaging [4]. Preoperative localization is advisable in patients proceeding to surgery, particularly when minimally invasive parathyroidectomy is planned. However, imaging studies are not recommended for diagnostic purposes alone, as their sensitivity and specificity are imperfect and false-positive rates can approach 25%.[104] In modern practice, minimally invasive parathyroidectomy is preferred in many centers. This focused procedure targets the specific hyperfunctioning gland identified on preoperative imaging and can be performed through a small incision with less tissue dissection, shorter operative time, and faster recovery.[161] Intraoperative PTH monitoring is widely used to verify surgical success. Since the half-life of PTH is only 3 to 4 minutes, an effective excision is indicated by a reduction in PTH of at least 50% from the pre-excision value within 10 to 20 minutes, typically accompanied by normalization or near-normalization of PTH levels within about 30 minutes.[162][163][164][165]

A small proportion of hyperfunctioning parathyroid tissue, approximately 2%, is located within the thyroid gland itself, most commonly as intrathyroidal adenomas.[166] These lesions may be detected and localized by ultrasonography or sestamibi scanning. Surgical management usually consists of targeted local excision of the adenoma or, if necessary, thyroid lobectomy, with high rates of cure.[166] For patients in whom standard surgery is contraindicated or refused, emerging techniques such as radiofrequency ablation of isolated parathyroid adenomas have been reported to provide effective control with minimal complications in small series.[167][168] While experience is still limited, this approach may represent a viable alternative for selected high-risk individuals who would otherwise remain untreated.[167] If primary hyperparathyroidism is left untreated, many patients will experience ongoing loss of cortical bone over time, increasing their risk of osteoporosis and fractures. By contrast, successful parathyroidectomy produces a substantial and durable increase in bone mineral density that can persist for up to 15 years or longer.[125][155] Patients with nephrolithiasis who

undergo curative surgery typically experience a reduction in stone formation, although they may still be susceptible to stones from other urinary risk factors. For this reason, a comprehensive 24-hour urinary stone risk profile is recommended after surgery to identify and manage additional lithogenic abnormalities.[148] During periods of nonoperative follow-up, progression of disease or the emergence of complications should prompt reassessment of the surgical option. Indications to reconsider surgery include low-trauma fractures, new or recurrent nephrolithiasis or nephrocalcinosis, persistent hypercalcemia with serum calcium more than 1 mg/dL above normal, significant decline in bone mineral density to a T-score below −2.5 at any site, or worsening renal function evidenced by a fall in creatinine clearance [4].

Hungry bone syndrome represents a distinctive postoperative complication following definitive surgical treatment of primary or secondary hyperparathyroidism. It is characterized by profound, prolonged hypocalcemia resulting from the abrupt withdrawal of PTH and the subsequent unopposed activity of osteoblasts, which rapidly incorporate circulating calcium into newly forming bone.[169][170] While definitions vary, most sources describe hungry bone syndrome as a serum calcium concentration below 8.4 mg/dL persisting for more than four days after successful parathyroid surgery.[169]170 This process is frequently accompanied by hypophosphatemia, hypomagnesemia, and significantly elevated alkaline phosphatase levels, reflecting intense bone formation and remodeling.[170] Hypocalcemia and hypophosphatemia may last for months or, in some cases, years.[170] It is important to distinguish hungry bone syndrome from other causes of hypocalcemia after parathyroidectomy, such as hypoparathyroidism or isolated hypomagnesemia. In postoperative hypoparathyroidism, serum phosphorus levels are typically high because PTH-mediated phosphaturia is absent, whereas in hungry bone syndrome, phosphorus tends to be low due to its uptake into bone.[169][170] The risk of hungry bone syndrome increases with the duration and severity of preoperative hyperparathyroidism, as well as in individuals with markedly elevated bone turnover and radiologic evidence of high-turnover bone disease.[169] The syndrome can also occur after treatment of other high bone turnover states, such as severe secondary hyperparathyroidism in dialysis patients, thyrotoxicosis, rapid vitamin D repletion in severely deficient individuals, or therapy for certain malignancies, including prostate cancer, that profoundly alter bone and mineral metabolism.[170][171] In contemporary practice, hungry bone syndrome is more commonly encountered after surgery for secondary hyperparathyroidism in patients with chronic renal failure than after operations for primary parathyroid disease [170].

Management of hungry bone syndrome centers on aggressive and prolonged calcium and vitamin D supplementation. High oral doses of calcium, often in the form of calcium citrate because of its superior absorption and tolerance, are typically required, along with active or nutritional vitamin D preparations to support calcium absorption and bone mineralization.[169][170] Intravenous calcium is indicated when serum calcium falls below approximately 7.6 mg/dL, when the patient develops clinical manifestations of hypocalcemia such as tetany, paresthesias, or seizures, or when electrocardiographic changes such as a prolonged QT interval are observed.[169][170][172] Calcium gluconate is generally preferred to calcium chloride for intravenous administration because it can be infused through a peripheral line and is less irritating to tissues, reducing the risk of local necrosis in the event of extravasation.[169][170][172] Close monitoring of serum calcium, phosphorus, magnesium, and alkaline phosphatase is essential, and supplementation is gradually tapered as bone remodeling stabilizes and calcium homeostasis returns to equilibrium. Further information regarding this complication and its management is available in the companion StatPearls article devoted to hungry bone syndrome [169].

Differential Diagnosis

The differential diagnosis of primary hyperparathyroidism is extensive, as many conditions can manifest with hypercalcemia or overlapping clinical features. Careful interpretation of biochemical profiles, along with targeted clinical assessment, generally allows for effective differentiation. Secondary hyperparathyroidism is an important consideration and typically arises in the context of chronic kidney disease or vitamin D deficiency. In this setting, PTH levels are elevated, but serum calcium is usually low or normal rather than frankly elevated, and hyperphosphatemia is commonly observed in renal failure. Normocalcemic primary hyperparathyroidism represents an early or attenuated form of parathyroid overactivity in which PTH is persistently elevated while total and ionized calcium levels remain within the normal range; secondary causes of increased PTH, such as vitamin D deficiency, must be excluded before this diagnosis is made. Familial hypocalciuric hypercalcemia also closely mimics primary hyperparathyroidism but is characterized by lifelong mild hypercalcemia, relatively low urinary calcium excretion, and typically benign clinical behavior; distinguishing this hereditary disorder from primary hyperparathyroidism is crucial, as surgery is not indicated in familial hypocalciuric hypercalcemia. Malignancy-related hypercalcemia, including humoral hypercalcemia of malignancy mediated by PTH-related protein, is a major alternative diagnosis.

These patients often have more acute and severe hypercalcemia, suppressed intact PTH levels, and clinical or radiologic evidence of an underlying neoplasm. Granulomatous diseases such as sarcoidosis and certain lymphomas may also cause hypercalcemia through increased extrarenal production of 1,25-dihydroxyvitamin D, leading to enhanced intestinal calcium absorption. Other endocrine and metabolic disorders must be considered, including hyperthyroidism, which can induce increased bone turnover and mild hypercalcemia, as well as the effects of lithium therapy, which shifts the set-point of the calcium-sensing receptor, and thiazide diuretics, which reduce urinary calcium excretion and can unmask underlying parathyroid disease. Metabolic conditions such as milk-alkali syndrome result from excessive ingestion of calcium and absorbable alkali and present with hypercalcemia, metabolic alkalosis, and renal impairment. Vitamin A intoxication and vitamin D intoxication can each cause hypercalcemia via increased bone resorption or excessive intestinal absorption, respectively. Through systematic evaluation of PTH levels, vitamin D metabolites, urinary calcium excretion, renal function, and relevant clinical history, clinicians can usually distinguish primary hyperparathyroidism from these alternative diagnoses and tailor management accordingly.

Prognosis

The prognosis of primary hyperparathyroidism depends on the severity of hypercalcemia, the presence of end-organ involvement, comorbid conditions, and whether definitive surgical treatment is undertaken. In the United States and other regions with routine biochemical screening, most patients are now diagnosed when an elevated serum calcium concentration is unexpectedly identified on a standard chemistry panel, often before significant symptoms or complications develop. Long-term observational studies of individuals with mild, asymptomatic primary hyperparathyroidism managed without surgery suggest that biochemical parameters, including serum calcium and PTH, remain relatively stable over time in approximately 80% of patients.[125] However, even in this apparently indolent group, bone mineral density tends to gradually decline, particularly at cortical sites, reflecting persistent PTH-mediated skeletal remodeling. This slow but progressive bone loss translates into an increased risk of osteopenia, osteoporosis, and fractures over the longer term. Patients with more substantial elevations of serum calcium are at higher risk for clinically significant complications, including nephrolithiasis, nephrocalcinosis, reduced renal function, and more pronounced skeletal disease. In such individuals, the natural history without intervention is less favorable, and parathyroid surgery is generally recommended to prevent further organ damage. Parathyroidectomy, when successfully performed, can permanently correct the underlying hormonal abnormality by removing the source of autonomous PTH secretion. This results in durable normalization of serum calcium levels and a substantial reduction in PTH concentrations.[125] Postoperatively, patients typically experience improvement in bone mineral density at multiple skeletal sites, with a corresponding reduction in fracture risk, as well as a lower incidence of nephrolithiasis due to decreased urinary calcium excretion.[125] The overall long-term outlook for patients who undergo successful parathyroidectomy is excellent, with high cure rates and significant reversal of many disease-related complications. Conversely, for patients managed conservatively, prognosis is generally acceptable in the short to intermediate term, but careful surveillance is necessary to detect biochemical or structural progression that may warrant reconsideration of surgery. Thus, prognosis in primary hyperparathyroidism is closely linked to early recognition, appropriate risk stratification, and timely selection of definitive surgical versus structured medical management based on established guidelines and individual patient factors.[125]

Complications

Primary hyperparathyroidism is associated with a broad spectrum of complications affecting the skeletal, renal, cardiovascular, gastrointestinal, and neuropsychiatric systems. One of the most clinically significant complications is the progressive loss of bone mineral density, particularly at cortical sites such as the distal radius and hip. Chronic PTH excess leads to increased bone turnover with net resorption, resulting in osteopenia, osteoporosis, and an elevated risk of fragility fractures. Patients may present with bone pain, skeletal deformities in advanced cases, or fractures involving the vertebrae, ribs, or long bones. Osteitis fibrosa cystica, although now rare in developed settings, represents an extreme manifestation of prolonged and untreated disease and is characterized by subperiosteal resorption, cystic bone lesions, and brown tumors. Renal complications are also prominent in the natural history of primary hyperparathyroidism. Hypercalciuria, present in a large proportion of patients, predisposes to nephrolithiasis, which may manifest as symptomatic renal colic, hematuria, or recurrent urinary tract infections. Over time, repeated stone formation or persistent intrarenal calcifications can lead to nephrocalcinosis, chronic kidney disease, and reduced glomerular filtration. Patients may also experience concentrating defects and polyuria due to hypercalcemia-induced nephrogenic diabetes insipidus. Even after successful parathyroidectomy, the risk of nephrolithiasis may not completely normalize, particularly if other lithogenic factors

remain, although stone frequency usually declines. Other complications reflect the systemic effects of hypercalcemia and PTH excess. Gastrointestinal manifestations include anorexia, nausea, constipation, abdominal pain, and, in some cases, pancreatitis or peptic ulcer disease. Neuropsychiatric complaints are common, encompassing fatigue, depression, anxiety, irritability, cognitive slowing, sleep disturbances, and headaches. These symptoms may be subtle and nonspecific but can significantly impair quality of life. Cardiovascular alterations such as hypertension, left ventricular hypertrophy, vascular calcification, and potential arrhythmias have been reported, though the extent to which they are directly attributable to primary hyperparathyroidism versus coexisting risk factors remains a subject of ongoing study. A notable iatrogenic complication is hungry bone syndrome, a profound and prolonged hypocalcemia that may occur after parathyroidectomy, especially in individuals with long-standing severe hyperparathyroidism and high bone turnover. This condition requires intensive postoperative management with calcium and vitamin D supplementation. Overall, the burden of complications underscores the importance of timely diagnosis, careful risk assessment, and appropriate definitive or medical treatment in patients with primary hyperparathyroidism.

Patient Education

Effective management of primary hyperparathyroidism relies heavily on comprehensive patient education and shared decision-making. Patients should be informed that multiple therapeutic strategies exist, ranging from active surgical intervention to careful medical surveillance, and that the optimal choice depends on disease severity, symptoms, comorbidities, age, and personal preferences. It is essential to emphasize that parathyroidectomy is the only definitive cure for primary hyperparathyroidism and that, in appropriately selected candidates, surgery is associated with very high success rates—curing more than 90% to 95% of patients when performed by experienced endocrine surgeons. Understanding this curative potential can help patients who are hesitant or fearful about surgery make more informed choices, particularly if they face elevated risks for fractures, nephrolithiasis, or other complications. At the same time, patients should be counseled about potential surgical risks, including postoperative hypocalcemia and hungry bone syndrome, especially in those with severe, long-standing disease or significant skeletal involvement. Preoperative discussion should cover the expected course of postoperative recovery, the need for serial calcium monitoring, and the possibility of temporary or prolonged calcium and vitamin D supplementation. Addressing these issues in advance can reduce anxiety and improve adherence to postoperative instructions. For patients managed medically, education should focus on the rationale for surveillance, the importance of regular follow-up, and the specific tests and imaging studies that will be used to monitor disease progression. Patients should understand the need for periodic measurements of serum calcium, PTH, and vitamin D, as well as renal function and bone mineral density, and how changes in these parameters could prompt reconsideration of surgical options. They should also be informed about lifestyle measures that support bone and renal health, including maintaining adequate hydration, engaging in weight-bearing exercise as tolerated, avoiding excessive dietary sodium and very high calcium intake from non-prescribed supplements, and moderating alcohol consumption. Moreover, patients should be made aware of symptoms that warrant prompt medical attention, such as acute flank pain suggestive of kidney stones, sudden worsening of bone pain, or signs of severe hypercalcemia like confusion, vomiting, or marked weakness. When pharmacologic therapies such as bisphosphonates, denosumab, or cinacalcet are used, education about potential side effects, adherence, and necessary laboratory monitoring is also vital. Through clear communication, written materials, and reinforcement at follow-up visits, clinicians can enhance patient engagement, support informed decision-making, and improve long-term outcomes in primary hyperparathyroidism.

Other Issues

Several key clinical insights can assist clinicians in the nuanced management of primary hyperparathyroidism. First, while classical teaching emphasizes the triad of hypercalcemia, hypophosphatemia, and elevated PTH, most contemporary patients actually present with normal serum phosphorus levels. Nevertheless, the coexistence of hypercalcemia with hypophosphatemia remains highly suggestive of primary hyperparathyroidism or related PTH-mediated processes and should prompt further evaluation for this diagnosis. A second important consideration is that hypovitaminosis D and dietary calcium deficiency can obscure or “mask” primary hyperparathyroidism.[173] In patients with elevated or borderline PTH levels but normal or low-normal calcium, a therapeutic trial of vitamin D and oral calcium supplementation can be instructive. In secondary hyperparathyroidism due to deficiency, PTH levels typically decline after repletion, whereas in primary hyperparathyroidism, PTH remains inappropriately elevated despite correction of these deficiencies.[62] All individuals with calcium-containing nephrolithiasis or nephrocalcinosis should be screened for hypercalcemia, and if present, PTH levels should be measured to evaluate for primary hyperparathyroidism as an underlying cause. From a skeletal perspective, primary hyperparathyroidism preferentially affects cortical bone, with relatively greater loss at sites such as the distal forearm, while

trabecular bone at the spine may be relatively spared. This pattern underscores the importance of three-site DEXA scanning, including the distal one-third radius, in addition to standard spine and hip measurements, to provide a more complete assessment of fracture risk.[155] Despite apparently preserved lumbar spine T-scores, patients may still have a substantial risk of vertebral fractures, some of which may be clinically silent. Neuropsychiatric manifestations constitute another important, and sometimes underappreciated, dimension of primary hyperparathyroidism. Many patients experience depression, anxiety, fatigue, irritability, lassitude, and sleep disturbances, which may be mistakenly attributed to aging, stress, or other comorbidities.[155][174][175][176] While some individuals report symptomatic improvement after parathyroidectomy, randomized and controlled studies have yielded inconsistent results, and current guidelines do not recommend surgery solely for neuropsychiatric indications in the absence of other criteria. In patients with a family history of hypercalcemia or hyperparathyroidism, clinicians should consider hereditary conditions such as multiple endocrine neoplasia types 1, 2A, or 4, as well as familial hypocalciuric hypercalcemia.[42] Measurement of urinary calcium excretion and calculation of the calcium clearance ratio offer a practical initial approach to differentiating familial hypocalciuric hypercalcemia from primary hyperparathyroidism.[42] When diagnostic uncertainty persists, genetic testing for mutations in the calcium-sensing receptor or other relevant genes can be pursued.[177] Patients with familial hypocalciuric hypercalcemia are typically asymptomatic, lack renal stones and significant skeletal disease, and do not benefit from parathyroid surgery, making accurate diagnosis crucial to avoid unnecessary intervention.

Enhancing Healthcare Team Outcomes

Optimizing outcomes for patients with primary hyperparathyroidism requires a coordinated, interprofessional approach that integrates the expertise of multiple healthcare professionals. Physicians, including endocrinologists, nephrologists, surgeons, radiologists, and primary care clinicians, play central roles in diagnosis, risk stratification, and treatment planning. Advanced practice practitioners, such as nurse practitioners and physician assistants, often facilitate longitudinal follow-up, patient education, and monitoring of laboratory and imaging studies. Nurses are critical in perioperative care, medication administration, symptom assessment, and reinforcement of lifestyle recommendations, while pharmacists contribute to medication reconciliation, identification of drug–drug interactions, and counseling on therapies such as cinacalcet, bisphosphonates, and vitamin D preparations. Effective interprofessional communication is fundamental to high-quality care. Regular case discussions, shared electronic health records, and clearly delineated roles support seamless transitions from diagnosis to treatment and long-term follow-up. For example, once biochemical evidence suggests primary hyperparathyroidism, collaboration between the endocrinologist, radiologist, and endocrine surgeon can streamline appropriate imaging, interpretation of localization studies, and selection of surgical approach. Postoperatively, close coordination between surgeons, medical teams, nurses, and dietitians is essential for monitoring calcium levels, recognizing early signs of hungry bone syndrome or hypocalcemia, and adjusting calcium and vitamin D supplementation. In patients managed conservatively, a shared-care model between specialists and primary care physicians supports adherence to monitoring guidelines, timely detection of disease progression, and reassessment of surgical candidacy when indicated. Ethical and patient-centered principles underpin all decision-making. Respect for patient autonomy is expressed through shared decision-making processes in which evidence-based recommendations are balanced with the patient's values, preferences, and life circumstances. For individuals with complex comorbidities or advanced age, the healthcare team must sensitively weigh the risks and benefits of surgery versus continued medical management, ensuring that patients and families understand the potential outcomes of each option. Care coordination is also vital when addressing comorbid conditions commonly associated with primary hyperparathyroidism, such as osteoporosis, chronic kidney disease, or cardiovascular risk factors. Ultimately, an organized, collaborative, and communicative interprofessional team can enhance safety, improve adherence, reduce duplication of tests, and deliver more holistic, patient-centered care, thereby improving both clinical outcomes and quality of life for individuals living with primary hyperparathyroidism.

Conclusion:

In conclusion, primary hyperparathyroidism is a disorder whose clinical presentation has evolved from overtly symptomatic to predominantly asymptomatic due to widespread biochemical screening. Its diagnosis hinges on demonstrating hypercalcemia with an inappropriately elevated parathyroid hormone level, followed by careful exclusion of secondary causes and familial hypocalciuric hypercalcemia. Management is not one-size-fits-all and must be personalized. Parathyroidectomy remains the definitive curative treatment and is clearly indicated for symptomatic patients and for asymptomatic individuals who meet specific criteria related to age, calcium level, renal function, bone density, or the presence of nephrolithiasis. For patients who do not meet these

surgical indications, a structured, conservative approach involving regular monitoring of serum calcium, renal function, and bone mineral density is safe and effective. Medical therapies, including antiresorptive agents and calcimimetics, play a crucial role in managing bone health and hypercalcemia in those who are not surgical candidates. Ultimately, optimal patient outcomes rely on a nuanced understanding of the disease spectrum, careful risk stratification, and a collaborative, interprofessional approach to guide treatment decisions and long-term follow-up.

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