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Review

Approach to the Diagnosis and Management of Primary Hyperparathyroidism

Layana Tyara Sandes Fraga *, Carlo Augusto Cicchetto Basílio and Monique Nakayama Ohe

Division of Endocrinology, Escola Paulista de Medicina, Universidade Federal de São Paulo—UNIFESP, São Paulo 04022-001, SP, Brazil; augusto.carlo94@gmail.com (C.A.C.B.); moniqueohe@gmail.com (M.N.O.)
* Correspondence: layanasandes@hotmail.com

Abstract

Primary hyperparathyroidism (PHPT) is a common endocrine disorder and an important cause of secondary osteoporosis, characterized by excessive or inappropriate parathyroid hormone secretion relative to serum calcium concentrations. Although its clinical presentation has shifted toward asymptomatic and mild biochemical phenotypes, skeletal and renal complications remain clinically relevant and may be overlooked. This narrative review discusses the diagnosis and management of PHPT, emphasizing diagnostic pitfalls, hereditary forms, and skeletal involvement. Biochemical assessment requires careful interpretation of calcium and parathyroid hormone measurements, recognition of preanalytical and immunoassay interference, and differentiation from familial hypocalciuric hypercalcemia and secondary causes of elevated parathyroid hormone. Normocalcemic PHPT requires rigorous exclusion of secondary hyperparathyroidism, and evidence guiding its treatment remains limited. Skeletal manifestations range from reduced bone mineral density and impaired cortical and trabecular microarchitecture to osteitis fibrosa cystica, brown tumors, and pathological fractures. Dual-energy X-ray absorptiometry, vertebral fracture assessment, and complementary tools such as trabecular bone score help characterize skeletal involvement beyond bone mass alone. Genetic evaluation in selected patients informs surgical planning, surveillance, and family screening. Parathyroidectomy remains the only curative treatment, whereas localization imaging serves surgical planning rather than diagnostic confirmation. For patients managed without surgery, antiresorptive agents improve bone mineral density, while cinacalcet controls hypercalcemia. Integrating accurate biochemical diagnosis, skeletal and renal assessment, and recognition of hereditary disease supports individualized management and helps avoid unnecessary investigations and inappropriate interventions.

Keywords: primary hyperparathyroidism; metabolic bone disease; osteoporosis; fracture risk; differential diagnosis; hereditary hyperparathyroidism; parathyroidectomy

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1. Introduction

Primary hyperparathyroidism (PHPT) is a hypercalcemic disorder characterized by excessive or inappropriate production of parathyroid hormone (PTH) in relation to the degree of hypercalcemia, by one or more parathyroid glands. The majority of PHPT cases are caused by a single benign adenoma (80–85% of cases), while multiglandular disease accounts for approximately 15–20% of patients. Parathyroid carcinoma is a rare condition, occurring in less than 1% of cases [1–3].

The clinical spectrum of PHPT ranges from asymptomatic presentations to disease with bone and renal involvement and symptoms associated with hypercalcemia [4,5].

Cardiovascular and metabolic changes [6], as well as neuropsychiatric manifestations [4,5], have also been described.

Over the past 50 years, the clinical spectrum of PHPT has shifted and is no longer predominantly highly symptomatic. Instead, oligosymptomatic or asymptomatic cases have become more frequent, both in developed and developing countries, due to greater availability of diagnostic methods and increased awareness of the disease among the medical community [2,4,7].

This change in the clinical presentation profile, while reflecting progress in medical practice through earlier diagnosis, can also generate greater diagnostic challenges due to the less clear signs and symptoms associated with this condition. This manuscript aims to address the diagnosis of PHPT, elucidating the main and potential pitfalls related to this process and thus contributing to the definition of more appropriate clinical approaches.

2. Epidemiology and Clinical Phenotypes

PHPT has an estimated prevalence of 23 cases per 10,000 women and 8.5 per 10,000 men, with an incidence of 66 cases per 100,000 person-years in women and 25 per 100,000 person-years in men in the United States [8,9]. It is a common disorder, ranking as the third most frequent endocrine disorder after diabetes mellitus and hypothyroidism, with a higher incidence mainly among postmenopausal women [10–12].

PHPT presents a heterogeneous clinical spectrum and can be classified into symptomatic, asymptomatic, and normocalcemic phenotypes [13,14]. Among symptomatic patients, the clinical presentation encompasses a variety of manifestations that can be categorized as classic or non-classic symptoms. Classic manifestations include bone disease (such as bone pain, pathological fractures, cysts, and brown tumors) and renal involvement (characterized by nephrolithiasis, nephrocalcinosis, and renal dysfunction), as well as symptoms related to hypercalcemia [4,5]. These are more common when serum calcium levels exceed 12 mg/dL or rise rapidly, and may include polyuria, polydipsia, constipation, anorexia, vomiting, dehydration, arrhythmias, and changes in mental status [14].

Non-classic symptoms are characterized by cardiovascular manifestations (atherosclerosis, arrhythmias, systemic arterial hypertension, and left ventricular hypertrophy), metabolic findings (insulin resistance and dyslipidemias) [6]; neurological manifestations may also occur, such as depression, anxiety, irritability, psychosis, delirium, cognitive impairment, and dementia [4,5].

In contrast, asymptomatic PHPT is characterized by the absence of clinically evident signs or symptoms, and is often identified incidentally through biochemical abnormalities on routine laboratory tests. In this context, evaluation of target organs helps distinguish patients with or without skeletal and/or renal involvement. Normocalcemic PHPT, in turn, is a specific biochemical phenotype in which bone and renal manifestations or complications may be present or absent [13,15].

3. Sporadic and Hereditary Forms

3.1. PHPT: Sporadic Form

PHPT can occur in either sporadic or hereditary forms. Sporadic PHPT is characterized by excess circulating PTH relative to serum calcium levels, in the absence of a family history of parathyroid tumors. It may result from either a parathyroid adenoma or carcinoma, and is caused by the accumulation of somatic mutations in parathyroid cells over time [8]. The molecular basis of sporadic PHPT mainly involves genetic and epigenetic alterations, with somatic mutations in the *MEN1* gene (30–40% of sporadic adenomas) and cyclin D1 overexpression (20–40% [12] and 10–40% [16]) being the main identified mechanisms.

3.2. PHPT: Hereditary Forms

Hereditary forms of PHPT account for 10% to 15% of cases, with variable penetrance, earlier onset, and a higher frequency of multiglandular disease compared to the sporadic form [8,17]. They are traditionally classified as syndromic, when PHPT is part of a set of endocrine or systemic manifestations, and non-syndromic, when the predominant involvement is restricted to the parathyroid glands [17,18]. The main genetic, clinical, and therapeutic features of selected hereditary forms of PHPT and familial hypocalciuric hypercalcemia are summarized in Table 1.

Table 1. Hereditary forms of primary hyperparathyroidism: genetic, clinical and therapeutic aspects.

DISEASE	GENE	INHERITANCE	CHARACTERISTICS OF PHPT	ASSOCIATED FEATURES	MANAGEMENT OF PHPT
SYNDROMIC FORMS					
MEN1	*MEN1*	AD	Early onset, high penetrance, and multiglandular disease; supernumerary and ectopic glands; frequent recurrence	Pituitary tumors, GEP-NETs	When surgery is indicated, bilateral neck exploration and subtotal parathyroidectomy, usually combined with transcervical thymectomy; long-term follow-up
MEN4	*CDKN1B*	AD	Generally milder phenotype and later onset than MEN1; often a single adenoma, although multiglandular disease may occur	Pituitary tumors, GEP-NETs	Individualized management; consider bilateral neck exploration because of the possibility of multiglandular disease; follow-up for recurrence
MEN2A	*RET*	AD	Earlier onset than sporadic PHPT; multiglandular disease should be considered	Medullary thyroid carcinoma and pheochromocytoma; occasionally cutaneous lichen amyloidosis and Hirschsprung disease	Bilateral neck exploration and resection of enlarged glands; prophylactic parathyroidectomy is not recommended
HPT-JT	*CDC73*	AD	Early onset; predominantly single-gland involvement, although asymmetric multiglandular disease may occur; 20–30% risk of parathyroid carcinoma	Ossifying jaw tumors, uterine tumors; renal tumors and cysts	Targeted parathyroidectomy for well-localized single-gland disease without suspected malignancy; oncologic en bloc resection if carcinoma is suspected; lifelong follow-up

Table 1. *Cont.*

DISEASE	GENE	INHERITANCE	CHARACTERISTICS OF PHPT	ASSOCIATED FEATURES	MANAGEMENT OF PHPT
NONSYNDROMIC FORMS					
FHH1	*CASR*	AD	Most common form, persistent mild hypercalcemia from childhood; hypocalciuria; inappropriately normal/mildly elevated PTH	Usually asymptomatic, minimal target organ effect	Conservative management; avoid parathyroidectomy
FHH2	*GNA11*	AD	Generally mild phenotype, similar to FHH1	Usually asymptomatic, minimal target organ effect	Conservative management; avoid parathyroidectomy
FHH3	*AP2S1*	AD	Generally the most severe form of FHH, with higher calcium and PTH levels, hypermagnesemia, and hypocalciuria	May be associated with target organ effects (low bone mineral density, osteomalacia, recurrent pancreatitis, and cognitive dysfunction)	Predominantly conservative management; avoid routine surgery. Consider cinacalcet for symptomatic disease and investigate a concomitant adenoma in the presence of target-organ damage
NEONATAL SEVERE HYPERPARATHYROIDISM (NSHPT)	*CASR*	AR	Severe neonatal hypercalcemia, markedly elevated PTH, and multiglandular hyperplasia; potentially fatal	Skeletal demineralization, fractures, thoracic deformities, hypotonia, and respiratory failure	Cinacalcet and/or a bisphosphonate may be used initially, but urgent total parathyroidectomy is usually required
FAMILIAL ISOLATED HYPERPARATHYROIDISM (FIHP)	*GCM2*	AD	Increased frequency of multiglandular disease, persistent disease, and possible carcinoma; higher preoperative PTH levels	No extraparathyroid manifestations	Parathyroidectomy with consideration of bilateral neck exploration

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; FHH, familial hypocalciuric hypercalcemia; FIHP, familial isolated hyperparathyroidism; PHPT, primary hyperparathyroidism; GEP-NETs, gastroenteropancreatic neuroendocrine tumors; HPT-JT, hyperparathyroidism-jaw tumor syndrome; MEN1, multiple endocrine neoplasia type 1; MEN2A, multiple endocrine neoplasia type 2A; MEN4, multiple endocrine neoplasia type 4; NSHPT, neonatal severe hyperparathyroidism; PTH, parathyroid hormone. Source: Table adapted and summarized from Jha and Simonds [8] and Grover and Jha [17].

Among the syndromic forms, multiple endocrine neoplasia type 1 (MEN1) stands out, caused by inactivating variants in the *MEN1* gene; multiple endocrine neoplasia type 2A (MEN2A), associated with activating variants in the *RET* gene; multiple endocrine neoplasia type 4 (MEN4), resulting from inactivating variants in *CDKN1B*; and hyperparathyroidism-jaw tumor syndrome (HPT-JT), related to inactivating variants in *CDC73* [17,19].

MEN1 is the most common syndromic cause and is characterized by early onset PHPT, high penetrance, and multiglandular involvement, mainly associated with gas-

troenteropancreatic neuroendocrine tumors, pituitary tumors, adrenocortical tumors, bronchial/thymic carcinoids, lipomas, and other skin lesions such as angiofibromas and collagenomas [8,20,21]. PHPT associated with MEN1 is a multiglandular disease, with a higher chance of recurrence even after subtotal parathyroidectomy [22,23]. Compared to sporadic PHPT, MEN1-related PHPT has an earlier age of onset, is often the first manifestation of the disease, affects almost 100% of patients by age 50, and frequently appears in adolescence [17,23,24].

In MEN2A, PHPT has lower penetrance, is usually milder, and occurs in association with medullary thyroid carcinoma and pheochromocytoma. Some patients may also present with cutaneous lichen amyloidosis and Hirschsprung's disease [8,17]. MEN4 has a phenotype similar to MEN1, though it is rarer, usually milder, and has a later onset. PHPT is the most frequent manifestation, generally due to a single adenoma, with low rates of multiglandular disease and recurrence [25]. In HPT-JT, parathyroid involvement is often uniglandular and asymmetric, but there is a substantial risk of parathyroid carcinoma (20–30%), in addition to the occurrence of ossifying fibromas of the jaws and renal and uterine tumors [8,17,18].

Other syndromic associations have been described more recently. Germline variants in *MAX*, classically related to hereditary pheochromocytoma and paraganglioma, have been identified in families with PHPT and other endocrine tumors, constituting a phenotype still under characterization, sometimes referred to as multiple endocrine neoplasia type 5 (MEN5) [26]. Parathyroid adenomas and carcinomas have also been reported in patients with Birt–Hogg–Dubé syndrome, associated with germline and somatic inactivating variants in the *FLCN* gene, and PHPT in individuals with X-linked intellectual disability syndrome caused by variants in the *ZFX* gene. However, these associations are based on a limited number of cases and do not yet have the same level of evidence as classic hereditary syndromes [17].

Non-syndromic forms include familial isolated hyperparathyroidism (FIHP), characterized by familial occurrence of PHPT without associated extraparathyroid manifestations. This is a genetically heterogeneous group, which may represent incomplete expression of variants in the *MEN1*, *CDC73*, or *CASR* genes, be associated with germline activating variants in *GCM2*, or remain without an identified genetic cause [8,27]. Familial hypocalciuric hypercalcemia (FHH) is an important hereditary differential diagnosis of PTH-dependent hypercalcemia. Its three recognized forms—FHH1, FHH2, and FHH3—are caused, respectively, by inactivating variants in the *CASR*, *GNA11*, and *AP2S1* genes. In general, they are characterized by persistent hypercalcemia from early ages, hypocalciuria, and normal or slightly elevated PTH concentrations, with FHH3 usually associated with more pronounced biochemical changes and clinical manifestations. Recognizing these conditions is essential to avoid unnecessary and, in most cases, ineffective parathyroidectomy [8,17].

Finally, neonatal severe hyperparathyroidism (NSHPT) is a potentially fatal condition, usually caused by biallelic inactivating variants in *CASR*, in homozygous or compound heterozygous form, inherited from parents with FHH1 [8,28]. It manifests within the first days to weeks of life with severe hypercalcemia, markedly elevated PTH concentrations, respiratory difficulty, chest deformities, hypotonia, and intense bone demineralization [8]. Most patients require urgent total parathyroidectomy [29].

3.3. Parathyroid Carcinoma

Parathyroid carcinoma (PC) is a rare condition, accounting for less than 1% of cases of PHPT. It is often classified as sporadic, although it may be part of familial syndromes. Unlike PHPT, PC does not show a predominance in females over males, and diagnosis usually occurs, on average, 10 years earlier than PHPT caused by benign disease [30].

The etiology is not fully understood and is generally sporadic, although specific syndromes may be associated with its development. Mutation in the *CDC73* gene is one of the most frequently found, occurring in up to 80% of sporadic cases. This explains the possible association between PC and HPT-JT, which also shows a strong correlation with mutation in this gene. Although *MEN1* mutations are more commonly associated with benign tumors, there are reports of patients with PC and this genetic mutation as well [31].

The clinical symptoms of PC are primarily determined by the effects of severe hypercalcemia and high PTH concentrations, rather than by local compression resulting from tumor growth. Hypercalcemia may present with serum concentrations higher than those observed in PHPT, often exceeding 14 mg/dL, which leads to clinical manifestations such as muscle weakness, polyuria, polydipsia, confusion, anorexia, and vomiting [32]. PTH concentrations can be 3 to 5 times the upper limit of normal, reaching values above 500–1000 pg/mL. In addition, laboratory tests may show elevated alkaline phosphatase levels, indicating the severity of skeletal involvement [32,33].

Skeletal manifestations are also expected in patients with PC and range from osteopenia/osteoporosis to pathological fracture [34]. There is a notable predominance of cortical involvement, which explains a significant reduction in bone mineral density (BMD) in the distal radius [35]. Other clinical findings may include nephrolithiasis, asthenia, the presence of a palpable mass in the cervical region, and neuropsychiatric manifestations. Although less common, symptoms related to the compressive effect of the tumor on cervical structures may also be present, such as hoarseness secondary to recurrent laryngeal nerve compression or dysphagia [32,33].

4. Diagnostic Evaluation

The diagnosis of hypercalcemic PHPT requires elevated albumin-adjusted serum calcium concentrations in the presence of elevated or inappropriately normal intact PTH concentrations on two occasions at least two weeks apart [13]. In PHPT, this increase in PTH, measured using second- or third-generation "sandwich" immunometric assays, occurs concurrently with hypercalcemia, which is preferably identified by measuring total plasma calcium. It should be noted that in about 10–20% of cases, this measurement may be at the upper limit of normal, requiring additional testing of ionized calcium, which is the biologically active form. Ionized calcium accounts for more than 50% of circulating levels, while the remainder is bound to albumin and other globulins [36]. Calcium measurements can be influenced by sample collection factors. Hemolysis and lack of fasting can falsely elevate total calcium levels, while clinical conditions with increased acidemia and venous stasis can cause lactic acid buildup, resulting in a falsely elevated ionized calcium level [37].

Immunoassays for PTH measurement are commonly used in diagnostic routines and are classified as second- or third-generation based on the affinity of the monoclonal antibody in the assay for recognizing amino acid residues of the PTH molecule. Second-generation assays use two distinct antibodies—one against the amino-terminal segment and another against the carboxy-terminal portion of PTH [38]. Third-generation immunometric assays, which measure biointact PTH, on the other hand, were developed to exclusively identify the biologically active form of PTH (1–84). In these assays, a specific antibody for the amino-terminal region—targeting the first four amino acids—is used to restrict measurement to the active molecular forms (1–84), thus not recognizing long fragments of the carboxy-terminal region [39].

These methods show excellent correlation with each other, and both are equally effective for diagnosing PHPT [40]. However, immunometric assays may be subject to pre-analytical factors such as improper sample storage, biotin contamination, or the presence of

heterophilic antibodies. Interference from these antibodies can lead to falsely elevated PTH measurements, potentially resulting in diagnostic errors [41].

Serum phosphorus concentrations are usually reduced or near the lower limit of reference (low normal). This finding is a consequence of the phosphaturic action of excess PTH, which inhibits tubular phosphate reabsorption in the kidneys. Although phosphorus measurement is not mandatory for diagnosing the condition, its assessment can provide relevant laboratory support in the diagnostic investigation of the disease. The evaluation of calciuria is a standard component of the workup and should preferably be performed by collecting 24 h urine, due to the circadian variability of calcium excretion. The mechanism of hypercalciuria in PHPT involves PTH stimulation of the renal 1-alpha-hydroxylase enzyme, which increases the production of 1,25-dihydroxyvitamin D [1,25$(OH)_2$D]. This active form of vitamin D increases intestinal calcium absorption, resulting in a greater renal calcium load that exceeds the tubular reabsorption capacity, despite the direct anticalciuric effect of PTH in the renal tubules [13].

The effects of PHPT on increased bone remodeling can be observed through measurement of bone biomarkers, where both procollagen type I N-terminal propeptide (P1NP), a highly sensitive biomarker for bone formation reflecting osteoblastic activity, and C-terminal telopeptide of type I collagen (CTX), the gold standard for assessing resorption reflecting collagen matrix breakdown by osteoclasts, are elevated. Given the pronounced acceleration of bone turnover caused by excess PTH in PHPT, evaluating these markers before surgical intervention is of interest. Baseline analysis of CTX and P1NP not only demonstrates the intensity of the metabolic disorder but also serves as a relevant prognostic predictor, since significantly elevated preoperative levels directly correlate with marked recovery of BMD in the femur and lumbar spine one year after successful parathyroidectomy [42].

5. Radiological Findings in PHPT

Chronic hypersecretion of PTH promotes a state of high bone turnover. In this condition, resorption exceeds formation, resulting in reduced BMD, compromised bone microarchitecture, and, consequently, greater vulnerability to fractures [43–45]. Thus, the spectrum of manifestations ranges from osteopenia/osteoporosis to more severe conditions, such as osteitis fibrosa cystica and brown tumors [1,44,46].

The term “osteitis fibrosa cystica” refers to the set of classic skeletal manifestations of severe PHPT. These manifestations are generally seen on radiological imaging and include: “salt and pepper” appearance of the skull, subperiosteal resorption of the distal phalanges, bone cysts, so-called “brown tumors,” “rugger-jersey” spine, and pathological fractures with skeletal deformities [1]. Currently, the occurrence of osteitis fibrosa cystica has become rare in places that use systematic biochemical calcium screening, with a prevalence of less than 5% in patients from Western Europe and North America. Due to this epidemiological shift, routine radiological investigation is no longer recommended in most reference centers [47] (Figures 1 and 2).

The brown tumor constitutes a non-neoplastic skeletal manifestation associated with severe and chronic states of hyperparathyroidism. Its development occurs through the exacerbation of osteoclastic activity mediated by high PTH levels, leading to severe bone resorption and the consequent replacement of mineral component by vascularized fibrous stroma. From a histological perspective, these lesions exhibit clusters of multinucleated giant cells among spindle-shaped cells, with the presence of microfractures and deposits of hemosiderin, the pigment responsible for the macroscopic brown coloration [49,50]. Despite its historical significance, the incidence of this condition in PHPT has decreased to levels between 0.5% and 4.5% in developed countries, as a result of early detection of the disease in subclinical stages. Clinically, these lesions may present as single or disseminated,

with a predilection for sites such as the pelvis, femur, costal arches, mandible, and distal radius. Symptoms such as localized or generalized bone pain occur in half of patients, and diagnosis may be elucidated after the occurrence of a pathological fracture [49,50] (Figures 3–5).



Figure 1. Radiograph of the left hand showing marked bone rarefaction, associated with subperiosteal resorption and the presence of a resorptive lesion at the level of the fourth metacarpal. Source: Reproduced from Morimitsu et al. [48].



Figure 2. Plain radiograph of the right wrist showing cystic lesions in the third metacarpal and distal third of the radius. Source: Reproduced from Morimitsu et al. [48].

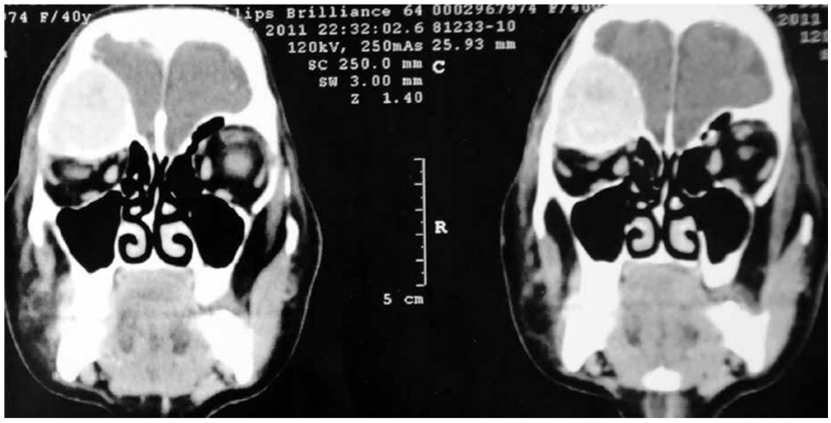


Figure 3. Computed tomography image showing an expansile lesion in the supraorbital region with features consistent with a brown tumor. Source: Reproduced from Ohe et al. [51].

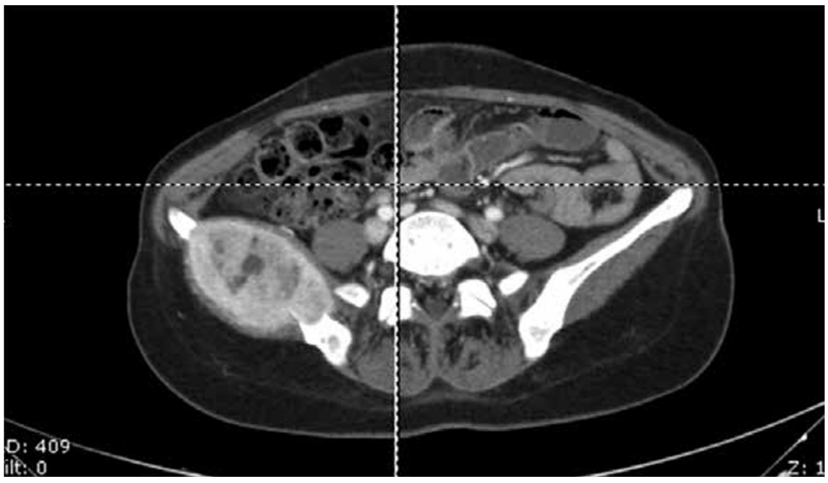


Figure 4. Computed tomography image showing a heterogeneous, expansile lesion in the ilium with features consistent with a brown tumor. Source: Reproduced from Ohe et al. [51].



Figure 5. Radiograph of the left femur showing a pathological fracture at the site of a preexisting bone cyst. Source: Reproduced from Morimitsu et al. [48].

6. Bone Density, Microarchitecture, and Fracture Risk

PHPT is a condition characterized by accelerated skeletal turnover, leading to progressive reduction in BMD, with a preference for cortical bone regions, and predisposing to a high risk of fractures at various anatomical sites [52]. The impact of PHPT on the skeleton is multifactorial and deleterious, resulting in decreased BMD—clinically manifested as osteoporosis or osteopenia—and a considerable increase in fracture risk. Although assessment tools such as the Fracture Risk Assessment Tool (FRAX) assume this risk is primarily mediated by reduced BMD, consistent epidemiological data demonstrate that PHPT establishes a state of bone fragility that goes beyond quantitative bone mass loss. Population studies show that individuals with PHPT face an increased risk for both hip fractures and major osteoporotic fractures, even among those under conservative management without immediate surgical indication. Furthermore, fracture risk may be underestimated in this population due to higher mortality risk from general causes, reducing life expectancy and thus attenuating the likelihood of experiencing a future fracture [53].

PHPT is associated with greater susceptibility to fractures in sites such as the spine, wrist, and pelvis. This increased risk is independent of BMD or clinical severity, indicating that fractures are influenced not only by reduced BMD but also by intense bone remodeling, as well as impaired bone quality and microarchitecture [54].

Given the limitations of traditional bone densitometry, dual-energy X-ray absorptiometry (DXA), in fully capturing fracture risk in PHPT, trabecular bone score (TBS) has emerged as a valuable complementary tool. TBS, through analysis of grayscale variation in the texture of the two-dimensional lumbar spine DXA image, serves as an indirect estimator of three-dimensional trabecular microarchitecture, reflecting structural quality and bone connectivity. This assessment allows for the identification of trabecular microarchitecture degradation even in patients whose lumbar spine BMD values are in the osteopenic or normal range. In practical terms, TBS provides an additional advantage over conventional DXA parameters for predicting morphometric vertebral fractures in PHPT [55].

Structural deterioration in PHPT, as evidenced by high-resolution peripheral quantitative computed tomography (HR-pQCT) analysis, occurs in a diffuse manner, extending beyond the cortex to profoundly affect the trabecular compartment. Under the influence of excess PTH, the destruction of plate-like trabeculae is observed, diminishing their connections and compromising skeletal rigidity, which is most prominent in the distal radius. Conversely, in the distal tibia, the hormone's catabolic impact on trabecular structure is attenuated, as the mechanical stress from weight-bearing plays a partially protective role. This generalized microarchitectural decline forms the biomechanical basis for the overall increased fracture risk, reinforcing that conventional two-dimensional DXA is limited in estimating actual bone fragility and quality in this condition [56].

7. Molecular Diagnosis

According to recommendations from the Fifth International Workshop on the Evaluation and Management of Primary Hyperparathyroidism, genetic testing should be considered in patients diagnosed with PHPT before the age of 30, those with multiglandular disease identified by clinical history, imaging studies, or during surgery, as well as individuals with a family history of hypercalcemia or hereditary syndromes associated with PHPT, such as MEN1, MEN2A, MEN4, and HPT-JT. Testing is also indicated in cases of atypical tumor or parathyroid carcinoma [13]. The possibility of a hereditary condition should also be considered in cases of PTH-dependent hypercalcemia with findings suggestive of FHH, such as mild, non-progressive, early-onset hypercalcemia, normal or mildly elevated PTH concentrations, and hypocalciuria without another apparent cause, particularly when the calcium-to-creatinine clearance ratio (CCCR) is less than 0.02, especially below 0.01 [17].

The choice of genes to be analyzed should be guided by the clinical criteria that prompted the investigation. In patients with suspected hereditary predisposition to PHPT, it is recommended to evaluate the *MEN1*, *CDC73*, *RET*, *CDKN1B*, *GCM2*, and *CASR* genes; in cases suggestive of FHH, *CASR*, *GNA11*, and *AP2S1* should be included. Since some patients may simultaneously meet criteria for both conditions, multigene panels that include all these genes can be used, allowing their simultaneous analysis by next-generation sequencing [57].

The identification of a germline variant can substantially change clinical and surgical management. In syndromes with a predisposition to multiglandular disease, for example, the result may indicate bilateral neck exploration and subtotal or total parathyroidectomy instead of a focal approach limited to the initially identified gland. In other situations, it may support earlier intervention due to a higher risk of parathyroid carcinoma, guide surveillance of extraparathyroid manifestations, or, in the case of FHH, avoid unnecessary and generally ineffective surgery. Moreover, molecular diagnosis enables cascade screening of family members, distinguishing those who need specific follow-up from those without increased genetic risk, and provides relevant information for reproductive planning [13,57].

8. Differential Diagnoses

The evaluation of hypercalcemia should aim to differentiate between PTH-dependent and PTH-independent causes (Table 2). In the first group, PHPT, tertiary hyperparathyroidism (associated with advanced chronic kidney disease), chronic lithium use, and FHH stand out. In contrast, among the PTH-independent causes, it is essential to rule out so-called "hypercalcemia of malignancy," and therefore, neoplasms must be excluded. In these cases, three different mechanisms predominate: production of parathyroid hormone-related peptide (PTHrP) (as occurs in breast, kidney, or lung cancer), overproduction of $1,25(OH)_2D$ (e.g., lymphomas), and lytic bone lesions secondary to metastases. In addition to neoplasms, other PTH-independent causes of hypercalcemia include granulomatous diseases, thyrotoxicosis, prolonged immobilization, or intoxication from vitamin A, cholecalciferol, or calcitriol [58].

Table 2. Differential diagnosis of hypercalcemia.

General Classification	Main Cause	Examples
PTH-dependent	Primary hyperparathyroidism	Adenoma; hyperplasia; carcinoma
	Tertiary hyperparathyroidism	Advanced chronic kidney Disease
	Genetic disorders	Familial hypocalciuric hypercalcemia (FHH)
	Drug-induced	Lithium
PTH-independent	Malignancy	Local osteolysis (bone metastases); PTH-related peptide (PTHrP) production; 1,25-dihydroxyvitamin D production
	Granulomatous diseases	Sarcoidosis; tuberculosis
	Endocrine disorders	Hyperthyroidism
	Drug-induced/toxic causes	Thiazide diuretics; vitamin D; calcium; vitamin A
	Other causes	Prolonged immobilization

Abbreviations: FHH, familial hypocalciuric hypercalcemia; PTH, parathyroid hormone; PTHrP, parathyroid hormone-related peptide. Source: Adapted from Maier and Levine [59].

The assessment of 24 h urinary calcium excretion is crucial to rule out an important differential diagnosis in clinical practice, FHH, in which the calcium/creatinine clearance ratio is typically less than 1%. On the other hand, patients with PHPT may have values >300 mg/24 h for men and >250 mg/24 h for women [60].

Lithium, an essential medication in the management of bipolar disorder, can influence serum calcium homeostasis. The drug can interfere with the calcium-sensing receptor (CaSR) present in the parathyroid glands, increasing the "set point" by which calcium inhibits PTH secretion. This calcilytic effect, antagonism at the CaSR, results in the need for higher serum calcium levels for the gland to reduce PTH synthesis and secretion. Consequently, patients on chronic lithium therapy may present with hypercalcemia associated with elevated PTH levels—a biochemical profile characteristic of PHPT. However, unlike classic PHPT, which is more often related to a parathyroid adenoma, prolonged lithium use can trigger hyperplasia of all four parathyroid glands [61,62].

Hypercalcemia of malignancy occurs in patients with a known cancer diagnosis or in those newly diagnosed after initial investigation prompted by elevated calcium levels. In this context, several pathophysiological mechanisms can explain the hypercalcemia, such as PTHrP production (common in solid tumors like breast, lung, and kidney), overproduction of $1,25(OH)_2D$ (lymphomas), and lytic bone lesions secondary to bone metastases [63].

In addition to malignancies, other conditions can cause hypercalcemia independent of PTH action, such as granulomatous diseases—for example, sarcoidosis, in which there is hyperactivity of 1-alpha-hydroxylase, the enzyme responsible for converting 25-hydroxyvitamin D [25(OH)D] into $1,25(OH)_2D$, the active form of vitamin D. Hyperthyroidism should also be considered, as thyroid hormone is responsible for increased bone resorption. Intoxication from cholecalciferol, calcitriol, or vitamin A, as well as the side effect of prolonged thiazide diuretic use, should also be considered. Vitamins A and D are fat-soluble and have a prolonged half-life, increasing the risk of persistent hypercalcemia as they are stored in adipose tissue [64].

A condition that deserves attention in biochemical investigation is normocalcemic hyperparathyroidism, which, as the name suggests, presents with elevated serum PTH levels but with repeatedly normal serum calcium values (both total and ionized) [65]. Normocalcemic hyperparathyroidism is characterized by elevated PTH levels in the presence of persistently normal serum calcium concentrations, both total and ionized. The diagnosis of this condition is fundamentally based on the exclusion of secondary causes of elevated PTH, requiring a careful investigation to rule out all possible causes of secondary hyperparathyroidism [66] (Figure 6).

Thus, it is essential to exclude factors such as vitamin D deficiency, low intake or poor absorption of calcium, renal insufficiency, and idiopathic hypercalciuria. In addition, the use of medications such as diuretics, bisphosphonates, and denosumab should be investigated, as well as the presence of gastrointestinal disorders, including celiac disease, inflammatory bowel diseases, and sequelae of bariatric surgery. There are also reports of interfering factors in the PTH assay, ranging from pre-analytical issues such as inadequate sample storage, to contamination by biotin, or the presence of heterophile antibodies. The interference of these antibodies may lead to a falsely elevated PTH measurement, which could induce diagnostic error.

Another often overlooked cause of isolated PTH elevation is primary aldosteronism (PA). PA is associated with significantly increased urinary calcium excretion and secondary hyperparathyroidism, which has been reported in approximately 30–55% of patients [67]. This phenomenon may result, at least in part, from reduced proximal tubular calcium reabsorption secondary to decreased sodium reabsorption, leading to increased urinary calcium losses and a compensatory rise in PTH levels. In addition, autonomous cortisol secretion,

which may coexist with PA, has been proposed as an additional contributor to disturbances in calcium and bone metabolism [68,69]. These and other abnormalities in mineral and bone metabolism may contribute to the increased risk of both nephrolithiasis [70,71] and fractures [72,73] observed in patients with PA. Importantly, specific treatment of PA can normalize PTH levels and improve mineral and bone metabolism, while reducing the risk of diagnostic confusion with conditions such as normocalcemic PHPT and thereby avoiding unnecessary investigations or interventions. Proper attention and exclusion of all these factors that can cause isolated elevation of PTH should be undertaken before diagnosing normocalcemic hyperparathyroidism, thus avoiding diagnostic errors and unnecessary therapeutic interventions [13,66].

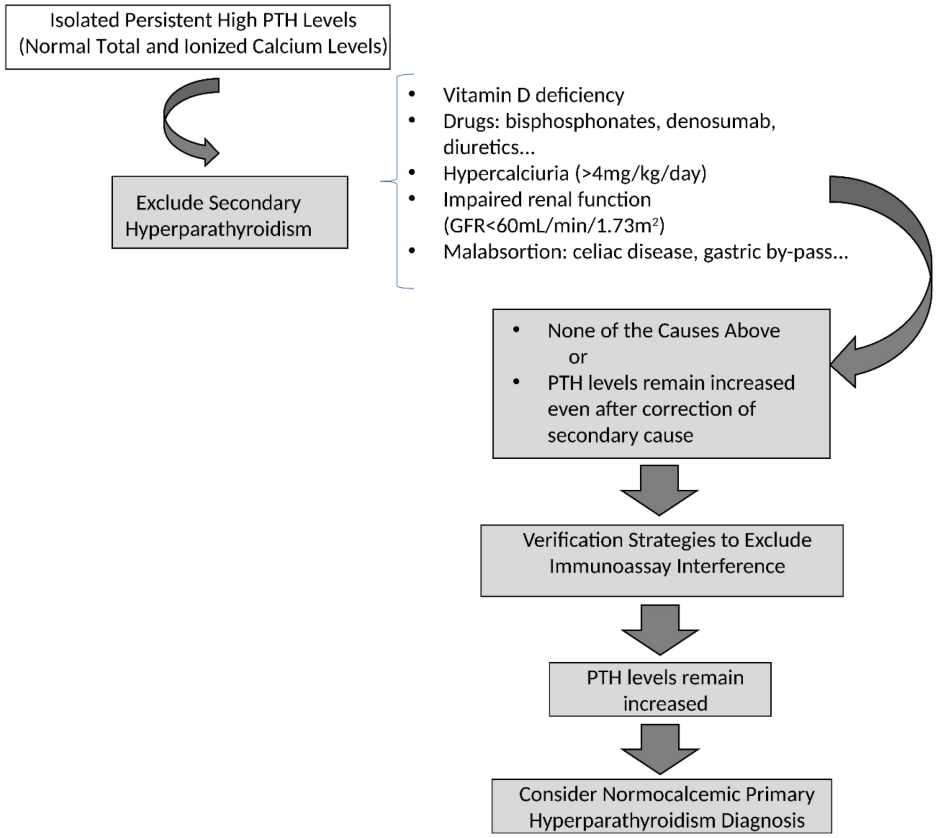


Figure 6. Differential diagnosis of high isolated parathyroid hormone (PTH) levels. Abbreviations: GFR, glomerular filtration rate; PTH, parathyroid hormone. Source: Reproduced from Ohe et al. [66].

9. Management

9.1. Surgical Treatment of Primary Hyperparathyroidism (PHPT)

The definitive treatment for PHPT is parathyroidectomy, with correct identification and removal of the affected parathyroid gland(s). Surgical indication is well established for symptomatic patients and those with renal and/or skeletal involvement, as these are the main candidates for surgery [74]. Thus, surgery is mandatory for symptomatic patients or for asymptomatic patients who meet specific criteria such as: serum calcium > 1.0 mg/dL above the upper limit of normal; skeletal involvement (vertebral fracture or T score ≤ −2.5 at any site); renal involvement (glomerular filtration rate < 60 mL/min, nephrolithiasis/nephrocalcinosis, or increased calciuria —>250 mg/day in women and >300 mg/day in men); or age < 50 years (Table 3) [74]. Interestingly, the technique involved in surgical treatment of PHPT has also changed over the years [75]. Driven by changes in clinical

presentation, with a greater number of oligo/asymptomatic cases, there has been a need to adapt the employed technique, involving a more focused approach, with shorter surgical time and lower risk of perioperative morbidity.

Table 3. Indications for surgery in asymptomatic PHPT.

Component	Clinical Criterion for Surgical Indication
Biochemical Parameters	Serum calcium levels exceeding the upper limit of normal by >1.0 mg/dL.
Bone Involvement	Presence of vertebral fracture (detected by X-ray or VFA) or T-score ≤ −2.5 at any anatomical site (lumbar spine, total hip, femoral neck, or distal radius).
Renal Involvement	Presence of at least one of the following findings: • Estimated glomerular filtration rate (eGFR) or creatinine clearance < 60 mL/min. • Presence of nephrolithiasis or nephrocalcinosis detected by any imaging method. • Significant hypercalciuria on 24-h urine collection: >250 mg/day in women or >300 mg/day in men.
Age Range	Patients younger than 50 years (age alone is already a sufficient indication).

Abbreviations: PHPT, primary hyperparathyroidism; VFA, vertebral fracture assessment; eGFR, estimated glomerular filtration rate. Source: Based on Bilezikian et al. [74].

Thus, the treatment of PHPT has evolved since the first successful parathyroidectomy performed by Felix Mandl in 1925 [76], which was initially described as a bilateral cervical exploration, and over the years has developed into a more focused approach [75]. It is important to note that 85% to 90% of PHPT cases are attributable to a single adenoma [77], and preoperative identification of abnormal glands allows for minimally invasive unilateral neck exploration, reducing operative time and surgical morbidity without compromising cure rates [78]. Recent parathyroidectomy techniques feature advances in preoperative localization exams to identify abnormal parathyroid glands as well as intraoperative PTH monitoring.

In cases of multiglandular disease, such as MEN1, the most commonly performed surgical technique—considered the "gold standard" today—is subtotal parathyroidectomy [79], in which part of the parathyroid tissue is preserved in situ. Other described techniques include total parathyroidectomy, total parathyroidectomy with autotransplantation of parathyroid tissue into the forearm or presternal muscle [80], and unilateral clearance, where the parathyroids on only one side are identified and removed [75,79]. These various surgical techniques are intended to minimize the risk of disease recurrence while also reducing the risk of postoperative hypoparathyroidism [75,79]. Each technique has its advantages and disadvantages, and discussion is needed to determine the best approach for individualized treatment of patients with multiglandular disease.

Regarding the management of normocalcemic PHPT, it should first be emphasized that this condition is relatively uncommon [65]. Moreover, studies addressing its management remain limited, and evidence-based criteria to guide either surgical or medical intervention are currently lacking. In the absence of robust data, current expert recommendations do not support the establishment of specific criteria for parathyroid surgery in this phenotype of PHPT [74].

Parathyroidectomy enables biochemical cure in more than 95% of patients, that is, it allows normalization of serum calcium, phosphorus, and PTH levels. The literature describes improvements in BMD in both the lumbar spine and femur, with benefits including reduced femur fracture rates in elderly patients [10,81,82].

A recent Cochrane review compared minimally invasive parathyroidectomy to bilateral exploration, showing that both approaches have excellent cure rates (96–99%) with no statistically significant difference. However, the literature also indicates that unilateral

exploration is associated with a lower incidence of complications, particularly transient hypocalcemia and recurrent laryngeal nerve injury [83,84].

Cure following parathyroidectomy is defined as normalization of serum calcium levels. This is expected to occur in more than 95% of cases when surgery is performed at a reference center. Recurrence can be classified as early, occurring within 5 years after surgery, or late, occurring after 5 years. Early recurrence is uncommon and is usually related to failure to identify multiglandular disease during surgery. An attenuated drop in intraoperative PTH or persistent elevation of serum PTH and calcium levels during follow-up may be indicative. Late recurrence, which is more prevalent, usually denotes a new pathological process in a previously healthy gland [10,85].

9.2. Adjunct Methods in Surgical Treatment

9.2.1. Parathyroid Localization

Preoperative localization studies include a combination of noninvasive and invasive imaging methods that identify abnormal parathyroid gland(s) and/or structures [75]. These tests neither confirm nor exclude the diagnosis of PHPT and should not be used to influence the surgical indication [77,82]. Localization imaging should be performed only after the surgical indication for parathyroidectomy has been established and is intended solely for surgical planning [82,86].

Cervical ultrasound is the most frequently requested localization test. It has the advantages of being noninvasive, not involving ionizing radiation, being less costly to health services, and having an accuracy of around 76% [86,87]. It also allows for the investigation of concomitant thyroid pathology [82,88].

Parathyroid scintigraphy with technetium-99m sestamibi (^{99m}Tc-MIBI), combined with single-photon emission computed tomography/computed tomography (SPECT/CT), is a functional imaging modality and is currently the gold standard for detecting hyperfunctioning parathyroid glands [75]. For example, a meta-analysis including 23 studies with 1236 patients showed a detection rate of 88% [87]. Cervical ultrasound is often used in combination with ^{99m}Tc-MIBI, and this association is considered the most cost-effective strategy for localizing hyperfunctioning parathyroid(s) both preoperatively and in cases of recurrence [82,86,88].

Four-dimensional computed tomography (4D-CT) consists of standard CT images with three vascular phases (unenhanced, arterial, and venous) and a fourth dimension that allows assessment of enhancement over time [89,90]. This technique can also provide functional data on enlarged parathyroid glands, where rapid uptake and washout of contrast is considered a typical feature of parathyroid adenoma [91], and it has localization rates comparable to those observed with ^{99m}Tc-MIBI [92].

Other tracers used in positron emission tomography/computed tomography (PET/CT), such as methionine [87] and choline, have emerged as better options than ^{99m}Tc-MIBI, with choline being the best among them, showing a sensitivity of 95% and a positive predictive value of 97% [93]. This technique can detect small adenomas less than 1.0 cm, which are often not localized by ^{99m}Tc-MIBI, but unfortunately it is expensive and still not available in our setting.

The accuracy of localization studies is higher in single-gland disease, while negative localization imaging is suggestive of the presence of multiglandular disease in PHPT [88,94].

Among the invasive methods, intraoperative PTH sampling from the internal jugular veins guided by ultrasound stands out, mainly indicated in cases of negative or discordant localization studies and is especially useful in reoperations [95]. This technique can assist in surgical decision-making by recognizing a PTH gradient, indicating the laterality of the hyperfunctioning gland [95]. There are few studies in the literature involving intra-

operative PTH sampling through bilateral central venous access. Initial reports date back to 1996, when Taylor et al. described the use of this technique in 21 patients with PHPT, achieving correct lateralization in 76% of cases [96]. However, this initial study did not yet define a sufficient cutoff value to categorize this lateralization. Only in 2007, when Ito et al. evaluated 216 patients with PHPT operated on with central intraoperative PTH measurement, did these authors manage to define a cutoff value. They considered a 5% difference between right and left jugular measurements for the PTH gradient sufficient to indicate lateralization and thus assist in locating the hypersecreting parathyroid, with a sensitivity of 78.9% [97]. The same authors demonstrated the safety of the method both intraoperatively and postoperatively, and its utility and safety have been observed in studies conducted at other medical centers [97,98].

The ideal sequence of preoperative imaging studies to be requested should be adapted according to the patient's needs, surgeon's preference, and availability of the various options. Repeating negative tests adds little information and further delays surgical resolution [86,99].

9.2.2. Intraoperative PTH

In 1991, Irvin et al. developed the rapid intraoperative PTH assay (IO-PTH) [100], and since 1996, IO-PTH has become commercially available and widely used by parathyroid surgeons worldwide [101–106], having been introduced in our setting in 2002 [103]. A significant percentage drop in IO-PTH, with a decrease of more than 50% from the pre-resection or pre-excision value of the supposedly hypersecreting parathyroid tissue, is indicative of surgical resolution [75]. On the other hand, absence of this decline indicates persistence of hypersecreting parathyroid tissue, requiring additional surgical exploration [75].

It was the combination of advances in the accuracy of preoperative localization imaging and intraoperative PTH measurement that made minimally invasive surgical techniques possible [75]. With this approach, surgery begins with resection of the previously localized gland and ends after confirmation of appropriate IO-PTH decline, without the need for bilateral exploration and identification of all other parathyroids [104]. This offers the advantage of lower perioperative morbidity and mortality while maintaining the same cure rates as bilateral exploration.

9.3. Clinical Treatment of PHPT

For patients who do not meet the criteria for parathyroidectomy or for those with contraindications to the procedure, clinical management is recommended, although it does not have a curative role like surgery. Clinical treatment consists of prescribing cinacalcet to reduce serum calcium levels, bisphosphonates or denosumab to improve BMD, together with adequate calcium intake and vitamin D repletion. Calcium restriction should be avoided because insufficient intake may further stimulate PTH secretion. Recommended total calcium intake is 800 mg/day for women younger than 50 years and men younger than 70 years, and 1000 mg/day for women older than 50 years and men older than 70 years, preferably from dietary sources, with supplements used when needed to meet these requirements. Vitamin D supplementation should be cautious to avoid worsening hypercalcemia, aiming to maintain serum 25(OH)D above 30 ng/mL and below the laboratory upper limit of normal (e.g., 50 ng/mL) [13,74].

The use of cinacalcet, a calcimimetic agent, quickly normalizes calcium levels in most patients and is associated with a reduction in PTH, with sustained long-term action, although the medication has no effect on BMD. On the other hand, bisphosphonates, such as alendronate, do not reduce serum calcium but do increase BMD in patients with PHPT.

Therefore, the combination of cinacalcet and bisphosphonates can be considered in clinical management [1,107].

Denosumab, a monoclonal antibody targeting receptor activator of nuclear factor-κB ligand, is a medication with proven benefits in increasing BMD in the lumbar spine and femoral neck. One study demonstrated a transient increase in PTH with the use of this medication; however, it offers potential control of calcemia when used in combination with cinacalcet [108].

PHPT is a well-established cause of secondary osteoporosis, with parathyroidectomy as its main therapeutic approach, providing increases of 3% to 4% in BMD in the first postoperative year. Nevertheless, many patients continue to have clinically significant skeletal fragility, and the efficacy of adjunctive pharmacotherapy in the postoperative period remains uncertain. Recently, Takebe and colleagues reported the first cases of postoperative use of romosozumab in patients with osteoporosis associated with PHPT, documenting significant gains of 25% to 30% in BMD, concentrated in the lumbar spine. Although preliminary, these findings suggest that sclerostin inhibition may be a potential anabolic strategy to optimize bone mass gain after surgical cure [109].

10. Conclusions

PHPT is a hypercalcemic disorder characterized by excessive or inappropriately elevated production of PTH, relative to the degree of hypercalcemia, by one or more parathyroid glands. It is a common condition, and its clinical presentation profile has changed over the last decades. Previously recognized as a predominantly symptomatic disease, it now more frequently presents as oligosymptomatic or asymptomatic forms, both in developed and developing countries.

The differential diagnosis involves investigating hypercalcemia to differentiate between PTH-dependent and PTH-independent causes, as well as investigating causes of isolated PTH elevation. The possibility of assay interference in PTH measurement must also be ruled out.

Localization imaging should be performed only after diagnostic confirmation and the indication for parathyroidectomy have been established, and its role is thus limited to strategic surgical planning, not to confirm or refute the diagnosis.

There are specific considerations regarding the management and surgical treatment of patients with genetic or syndromic forms of PHPT, a condition that should be especially suspected in young individuals diagnosed with PHPT. A hereditary etiology should be particularly suspected in young individuals diagnosed with PHPT. In hereditary syndromes associated with multiglandular disease, particularly MEN1, bilateral neck exploration is often appropriate; however, the surgical strategy should be individualized according to the syndrome, gland involvement, and risk of malignancy. Recognition of FHH is essential to avoid unnecessary parathyroidectomy.

Curative treatment consists of parathyroidectomy. When performed by experienced surgeons and combined with the use of adjuncts such as preoperative localization studies and intraoperative PTH measurement, surgery achieves cure rates of 96% to 99%, both through bilateral neck exploration and minimally invasive parathyroidectomy.

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