

Primary Hyperparathyroidism: An Updated Review

Salma Zniber^{1*}, Zineb Baba¹, Ahmed Mougui¹, Ahlam Belkhou¹

¹Department of Rheumatology, Mohammed VI University Hospital, Faculty of Medicine and Pharmacy, Cadi Ayyad University, Marrakech, Morocco

DOI: <https://doi.org/10.36347/sasjm.2026.v12i10.015>

| Received: 18.08.2026 | Accepted: 20.10.2026 | Published: 24.10.2026

*Corresponding author: Salma Zniber

Department of Rheumatology, Mohammed VI University Hospital, Faculty of Medicine and Pharmacy, Cadi Ayyad University, Marrakech, Morocco

Abstract

Review Article

Primary hyperparathyroidism (PHPT) is an endocrine disorder characterized by inappropriate, autonomous secretion of parathyroid hormone (PTH), leading to chronic hypercalcemia. It is the third most common endocrinopathy after diabetes mellitus and thyroid disorders. Since the widespread use of automated serum calcium measurement, classical symptomatic forms such as osteitis fibrosa cystica and recurrent nephrolithiasis have become rare, and most patients are now diagnosed at an asymptomatic stage, often during an osteoporosis work-up or following incidental hypercalcemia. The Fifth International Workshop (2022) distinguishes three entities: symptomatic hypercalcemic PHPT, asymptomatic hypercalcemic PHPT with or without targetorgan involvement, and normocalcemic PHPT. The diagnosis is exclusively biochemical, based on hypercalcemia (albumin-corrected or ionized calcium) with an elevated or inappropriately normal PTH, after exclusion of familial hypocalciuric hypercalcemia, vitamin D deficiency and renal impairment. Target-organ assessment includes 24-hour urinary calcium, estimated glomerular filtration rate, renal imaging, bone densitometry at three sites including the distal one-third radius, and vertebral imaging. Localization studies (neck ultrasound, ^{99m}Tcsestamibi scintigraphy with SPECT/CT, 4D-CT, ¹⁸F-fluorocholine PET/CT) have no diagnostic value and are indicated only before surgery. Parathyroidectomy remains the only curative treatment; its indications were updated in 2022, notably with a lower 24-hour urinary calcium threshold (250 mg/day in women and 300 mg/day in men instead of 400 mg/day). Medical therapy (bisphosphonates, denosumab, cinacalcet) is reserved for patients who are not surgical candidates or who decline surgery, and non-operated patients require regular clinical, biochemical and densitometric follow-up.

Keywords: Hypercalcemia; Osteoporosis; Parathyroid Hormone; Parathyroidectomy; Primary Hyperparathyroidism.

Copyright © 2026 The Author(s): This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CC BY-NC 4.0) which permits unrestricted use, distribution, and reproduction in any medium for non-commercial use provided the original author and source are credited.

1. INTRODUCTION

Primary hyperparathyroidism (PHPT) is an endocrine disorder characterized by inappropriate and autonomous secretion of parathyroid hormone (PTH), resulting in chronic hypercalcemia. After diabetes mellitus and thyroid disorders, it is the third most common endocrinopathy [2,9].

Historically described as a florid disease marked by nephrolithiasis and osteitis fibrosa cystica, PHPT is now most often discovered incidentally on routine laboratory testing, owing to automated serum calcium measurement. Most patients are therefore asymptomatic or have only subtle manifestations, such as osteopenia or mild neurocognitive complaints [2,3,9].

The clinical relevance of PHPT lies in its potential complications:

- **Skeletal:** predominantly cortical osteoporosis and fragility fractures;
- **Renal:** nephrolithiasis, nephrocalcinosis and chronic kidney disease;
- **Cardiovascular and neuropsychiatric:** still debated, but increasingly reported [3,9].

The most recent international recommendations the Fifth International Workshop (2022) and the American Association of Endocrine Surgeons (AAES) guidelines are based on risk stratification aimed at answering a single question: should this patient undergo surgery, or can he or she be monitored? The choice between parathyroidectomy and surveillance therefore depends not only on the presence of symptoms, but on target-organ involvement, biochemical severity and age

[1,5,7]. PHPT thus lies at the crossroads of endocrine, metabolic and bone disease, and warrants multidisciplinary management.

2. Epidemiology

2.1. Prevalence and incidence

The overall prevalence is estimated at 0.3% to 0.7% of the adult population, with a clear increase in older individuals [2].

In postmenopausal women it reaches 2% to 3%, partly reflecting the more frequent measurement of serum calcium during osteoporosis work-up [2,9].

Annual incidence varies widely according to region and screening practices, between 20 and 30 cases per 100,000 inhabitants in most series, with markedly higher figures in extensively screened populations [2,12].

These differences reflect the intensity of biochemical screening more than true differences in disease frequency. In countries where serum calcium is not routinely measured, PHPT is still diagnosed at a symptomatic skeletal or renal stage [2,8].

2.2. Risk factors

- **Female sex:** women are affected three to four times more often than men, particularly after menopause [8,9].
- **Age:** the disease is rare before 40 years, with a peak between 55 and 70 years [2].
- **Genetics:** familial forms occur in multiple endocrine neoplasia (MEN1, MEN2A), hyperparathyroidism–jaw tumor syndrome and familial isolated hyperparathyroidism. They account for fewer than 5% of cases [2,14].
- **Environmental and iatrogenic factors:** associations have been reported with chronic lithium exposure, thiazide diuretics, neck irradiation and prolonged vitamin D deficiency [2,9].

3. Pathology

In the vast majority of cases, PHPT results from a benign proliferation of the parathyroid glands, although several pathological substrates are possible.

3.1. Parathyroid adenoma

Adenoma accounts for 80% to 85% of cases. It is usually a single, benign and sporadic lesion responsible for autonomous PTH secretion. Adenomas are often small, well encapsulated and composed mainly of chief cells. Multiple adenomas are rare but more frequent in familial or lithium-associated forms [2,9].

3.2. Parathyroid hyperplasia

Hyperplasia is present in 10% to 15% of cases. It corresponds to diffuse, multiglandular and sometimes asymmetric involvement, and is frequently found in familial forms, particularly in multiple endocrine neoplasia types 1 and 2A [2,14]. The distinction from

secondary hyperparathyroidism may be difficult on histology alone and requires clinical and biochemical correlation [2,8].

3.3. Parathyroid carcinoma

Carcinoma is exceptional, accounting for less than 1% of PHPT. It should be suspected in the presence of a hard, fixed cervical mass, severe hypercalcemia and a markedly elevated PTH level, often three to ten times the upper limit of normal [2,9]. Histologically, it is characterized by capsular, vascular or perineural invasion. The diagnosis is often retrospective, made on local recurrence or metastases. Somatic or germline mutations of the CDC73 gene are frequently found [2].

3.4. Genetic and syndromic forms

Mutations in the MEN1, RET (MEN2A), CDC73 (HRPT2), CASR and GCM2 genes are involved in familial forms of PHPT [2,14]. These forms account for approximately 2% to 5% of cases. They should be suspected in the presence of a family history, young age at diagnosis, multiglandular or recurrent disease, carcinoma or atypical adenoma, or association with other endocrine tumors [1,2,14].

4. Physiology and Pathophysiology

4.1. Synthesis and secretion of parathyroid hormone

PTH is an 84-amino-acid polypeptide synthesized as a precursor, pre-pro-PTH, which is successively cleaved into pro-PTH and then mature PTH, stored and secreted by the chief cells of the parathyroid glands. Part of the newly synthesized PTH is degraded in lysosomes, while another part is cleaved by cathepsins into carboxy-terminal fragments that may be secreted. This mechanism, which depends on the extracellular ionized calcium concentration, contributes to the fine regulation of the amount of biologically active PTH released into the circulation [2,9].

4.2. Regulation by the calcium-sensing receptor and the concept of "set point"

PTH secretion is controlled by the calcium-sensing receptor (CaSR), a G protein-coupled receptor expressed on the surface of parathyroid cells. An increase in extracellular ionized calcium activates the CaSR and inhibits PTH release; conversely, hypocalcemia removes this inhibition and stimulates secretion [2,9].

The relationship between ionized calcium and PTH secretion is not linear but follows an inverse sigmoidal curve. The "set point" is the ionized calcium concentration at which PTH secretion is half-maximal. It defines the sensitivity threshold of the gland to calcium and is the key determinant of calcium–phosphate homeostasis, as it sets the serum calcium level around which the system stabilizes. In healthy individuals, the set point lies within the physiological range of ionized calcium, which keeps serum calcium within a narrow interval [2].

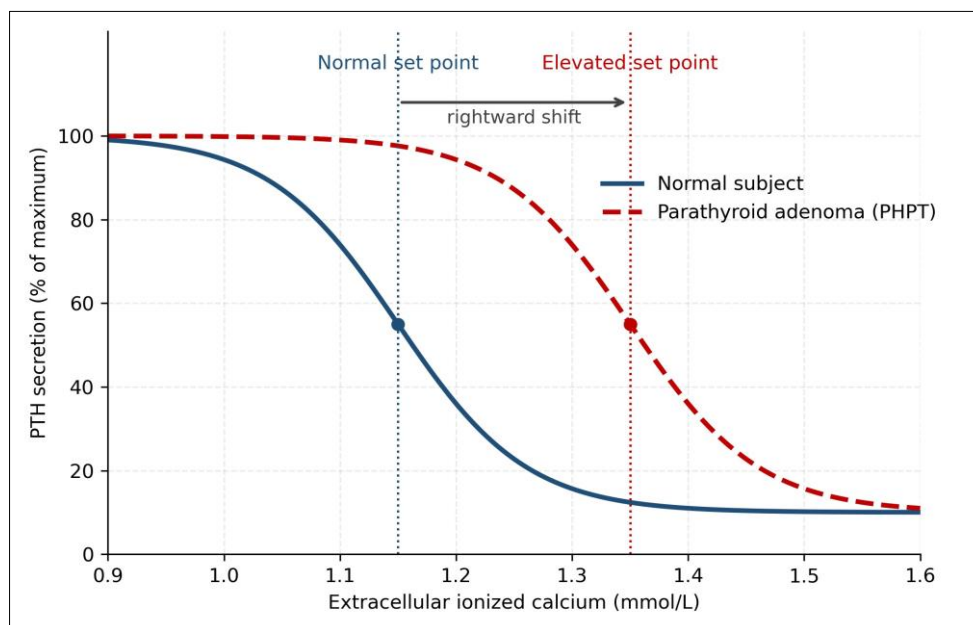


Figure 1: Sigmoidal relationship between extracellular ionized calcium and PTH secretion. In primary hyperparathyroidism, the curve is shifted to the right: a higher calcium concentration is required to suppress PTH secretion by half (elevated set point)

4.3. Biological effects of PTH

PTH acts by binding to its specific receptor, PTHR1, a G protein-coupled receptor expressed mainly by osteoblasts and renal tubular cells. This binding activates the classical adenylate cyclase and phospholipase C pathways, as well as non-classical pathways involving ERK kinases, phospholipase A2 and phospholipase D [2,9].

In bone, PTH does not act directly on osteoclasts, which do not express its receptor, but on osteoblasts. These increase the production of receptor activator of nuclear factor kappa-B ligand (RANKL) and macrophage colony-stimulating factor (M-CSF), while reducing osteoprotegerin (OPG) synthesis. The resulting activation of the RANK/RANKL pathway promotes osteoclast differentiation and activation, increasing bone resorption and releasing calcium and phosphate into the circulation. PTH also stimulates the production of proresorptive cytokines, notably interleukin-1, interleukin-6 and tumor necrosis factor-alpha [2,3].

In the kidney, PTH increases calcium reabsorption in the distal convoluted tubule, decreases phosphate reabsorption in the proximal tubule hence its phosphaturic effect and stimulates cyclic AMP, the second messenger of its tubular effects. It also activates 1-alpha-hydroxylase, the enzyme that converts 25-hydroxyvitamin D into 1,25-dihydroxyvitamin D (calcitriol) [2,9].

In the intestine, the effect of PTH is indirect: increased calcitriol enhances intestinal absorption of calcium and, to a lesser extent, phosphate [2,9].

4.4. Pathophysiological mechanisms of PHPT: elevation of the set point

The pathophysiology of PHPT is based on loss of the feedback control of serum calcium on PTH secretion. In parathyroid adenomas, CaSR expression is reduced on the surface of tumor cells: the sigmoidal curve is shifted to the right, meaning that the set point is elevated (Figure 1). A higher-than-normal calcium level is then required to achieve the same degree of suppression, and PTH secretion becomes inappropriate for the circulating calcium level [2,9].

In hyperplasia, increased secretion is related more to the expanded mass of secreting cells than to abnormal calcium sensitivity; the residual non-suppressible secretion of each cell becomes, by summation, quantitatively excessive [2].

This chronic hypersecretion leads to persistent hypercalcemia and hypophosphatemia. Its prolonged effects on bone, kidney and intestine account for the classical complications of the disease, particularly skeletal involvement cortical osteoporosis, osteitis fibrosa cystica and renal involvement nephrolithiasis, nephrocalcinosis [2,3].

5. Positive Diagnosis

5.1. Circumstances of discovery and current classification

The Fifth International Workshop (2022) clarified the definition of the various presentations of the disease and distinguishes three entities [1]:

- **Symptomatic hypercalcemic PHPT:** clinical manifestations directly attributable to hypercalcemia or target-organ involvement

symptomatic nephrolithiasis, fragility fracture, osteitis fibrosa cystica, hypercalcemic crisis.

- **Asymptomatic hypercalcemic PHPT, with or without target-organ involvement:** no symptoms, with organ involvement systematically sought by bone densitometry, vertebral imaging and renal imaging. This distinction is decisive, as the discovery of subclinical involvement shifts the indication toward surgery.
- **Normocalcemic PHPT:** persistently elevated PTH with normal albumin-corrected total and ionized calcium, after formal exclusion of all causes of secondary hyperparathyroidism [1,13].

5.2. The asymptomatic form

The asymptomatic form is now the most frequent presentation in countries where serum calcium is widely measured. It is typically discovered during a routine check-up, an osteoporosis work-up or following incidental hypercalcemia [1,3,9].

The term "asymptomatic" should, however, be qualified on three counts.

It does not mean "without organ involvement." Systematic assessment by three-site densitometry, vertebral imaging and renal imaging reclassifies a substantial proportion of patients initially labeled asymptomatic as having target-organ involvement, through the discovery of morphometric vertebral fractures or silent kidney stones [1,3].

It does not mean "without impact." These patients frequently report fatigue, diffuse pain or concentration difficulties, which are nonspecific but sometimes improve after surgery [3,15].

It does not mean "stable." Natural history studies show that some non-operated patients develop a surgical criterion during follow-up, hence the need for prolonged surveillance [1,5].

5.3. Clinical manifestations: nonspecific symptoms

One point must be emphasized at the outset: the symptoms of PHPT are nonspecific. None of them, taken in isolation, suggests the diagnosis, which remains biochemical. Their relevance is twofold: they may raise suspicion in a suggestive context, and their possible resolution after parathyroidectomy provides retrospective evidence of their attribution [3,9].

General and neuropsychiatric manifestations include persistent fatigue, proximal muscle weakness and impaired concentration or memory. These symptoms may mimic or accompany fibromyalgia or depression, which explains diagnostic delays. More overt signs lethargy, confusion, irritability are seen with marked hypercalcemia and usually improve after surgery [3,15].

Gastrointestinal manifestations include anorexia, constipation, abdominal pain or nausea, and more rarely acute pancreatitis or peptic ulcer disease [3,9].

Cardiovascular manifestations: PHPT has been associated with an increased risk of hypertension, left ventricular hypertrophy and arrhythmias. Causality and reversibility after surgery remain debated, and these features alone do not constitute an indication for surgery [1,3].

5.4. Renal manifestations

Renal involvement results from two intertwined mechanisms: the direct effects of hypercalcemia and the chronic tubular action of PTH. The functional signs of hypercalcemia polyuria, polydipsia, dehydration therefore belong to the same pathophysiological framework as nephrolithiasis [3,9].

Calcium nephrolithiasis is the classical expression of the disease. It results from hypercalciuria, a consequence of the increased filtered calcium load and stimulation of calcitriol synthesis, which outweigh the hypocalciuric tubular effect of PTH. It presents as recurrent renal colic or is discovered incidentally on imaging. Nephrocalcinosis, which is less common and often bilateral, may progress to chronic kidney disease if unrecognized [3,8].

Nephrolithiasis, symptomatic or silent, affects about 15% to 20% of patients in contemporary series, a large proportion being detected only by systematic imaging [1,3]. For this reason, every confirmed case of PHPT should undergo renal imaging and 24-hour urinary calcium measurement, even in the absence of urinary symptoms [1,7].

5.5. Skeletal manifestations

Skeletal manifestations have become less florid because of earlier diagnosis, but they retain major diagnostic and prognostic value and are the main reason for referral to a rheumatologist.

Chronic PTH excess causes resorption predominantly of cortical bone, resulting in predominantly cortical osteoporosis and, in long-standing severe forms, osteitis fibrosa cystica. Trabecular bone is relatively spared, which explains the characteristic densitometric profile, with marked involvement of the distal one-third radius contrasting with relative preservation of the lumbar spine. This profile justifies systematic bone mineral density measurement at three sites, including the radius [1,3].

Clinically, patients may report diffuse bone pain, mainly affecting the spine, pelvis and lower limbs, or localized pain related to a fragility fracture [3,15]. Fracture risk is increased, including in forms considered asymptomatic, and vertebral fractures are frequently

morphometric, hence the value of systematic vertebral imaging [1,3].

5.6. Articular manifestations

PHPT may present with diffuse arthralgia and episodes of acute arthritis. These manifestations are most often related to calcium pyrophosphate deposition disease, PHPT being one of the best-established metabolic causes of chondrocalcinosis [15,16,23].

The clinical expression is polymorphic: pseudogout attacks, chronic destructive arthropathy, or misleading presentations mimicking polyarthritis or polymyalgia rheumatica. An acute attack may also be triggered in the immediate postoperative period after parathyroidectomy [15,23]. This association justifies measuring serum calcium in any patient with chondrocalcinosis, particularly before the age of 60 [16,23].

Finally, some studies report a clinical overlap between PHPT and chronic widespread pain syndromes, notably in normocalcemic or mildly hypercalcemic forms [3,15].

5.7. Biochemical confirmation

The diagnosis is biochemical and relies on a pair of measurements:

- **Albumin-corrected total serum calcium**, ideally complemented by **ionized calcium**, which remains the reference in case of protein abnormalities;
- **Intact PTH (1-84; second- or third-generation assay)**, elevated or "inappropriate," that is, high-normal when it should be suppressed by hypercalcemia.

First-line testing also includes serum phosphate typically low or low-normal —, 25hydroxyvitamin D, serum creatinine with estimated glomerular filtration rate, and 24-hour urinary calcium. Bone-specific alkaline phosphatase and bone turnover markers are elevated in forms with marked skeletal involvement [1,8].

Two pitfalls must be systematically excluded before concluding: vitamin D deficiency, which raises PTH and may mask hypercalcemia, and renal

impairment, which raises PTH independently of PHPT. Vitamin D deficiency should be corrected before any definitive interpretation, particularly when normocalcemic PHPT is suspected [1,8,13].

5.8. Radiological manifestations

Radiological abnormalities reflect excessive and prolonged bone remodeling. They are now rarely seen in their complete form, but remain highly suggestive when present.

The earliest and most specific sign is subperiosteal resorption, visible on the radial aspect of the middle and proximal phalanges of the second and third fingers (Figure 3). Other forms of resorption may be observed: intracortical, giving a striated or tunneled appearance of the cortex; endosteal, causing scalloping of the cortex; and subchondral resorption, notably at the acromioclavicular and sacroiliac joints and the pubic symphysis [15].

In the skull, the coexistence of areas of demineralization and sclerosis within the trabecular network produces the classical "salt and pepper" appearance (Figure 2). In the jaws, thinning or disappearance of the lamina dura around the tooth roots may be observed.

In advanced forms, brown tumors appear: focal lytic lesions in which bone is replaced by fibrous tissue rich in giant cells, preferentially located in the mandible, ribs, pelvis and femur. They may mimic metastases or a primary bone tumor and represent a classical diagnostic pitfall [15].

Finally, imaging shows predominantly cortical osteopenia, diffuse cortical thinning and, when chondrocalcinosis is associated, cartilage calcifications of the menisci, the triangular fibrocartilage of the wrist and the pubic symphysis [15,16].

Beyond plain radiography, techniques assessing bone microarchitecture and quality trabecular bone score and high-resolution peripheral quantitative computed tomography reveal trabecular impairment and increased cortical porosity that are not detected by conventional densitometry, and allow better assessment of fracture risk [1,3].



Figure 2: Microlacunar appearance of the skull vault producing the "salt and pepper" pattern.



Figure 3: Subperiosteal bone resorption on the radial aspect of the phalanges

6. Etiological Diagnosis and Preoperative Localization

6.1. Principle

One point must be emphasized from the outset: parathyroid imaging has no diagnostic value. It neither confirms nor rules out PHPT, whose diagnosis is exclusively biochemical. It is indicated only once the decision to operate has been made, with the sole aim of guiding surgery. Negative imaging does not call the diagnosis into question and does not contraindicate surgery, which then relies on bilateral neck exploration [1,4,7].

6.2. First-line imaging

Neck ultrasound is the first-line examination: it is non-irradiating, accessible and inexpensive, and simultaneously assesses the thyroid useful information if a combined procedure is required. Its sensitivity, highly dependent on the operator and lesion location, is limited for ectopic, retroesophageal or mediastinal adenomas [4,7].

^{99m}Tc -sestamibi scintigraphy, performed as a dual-phase study and ideally combined with single-photon emission computed tomography/computed tomography (SPECT/CT), possibly with ^{123}I subtraction, provides better anatomical localization and allows

detection of ectopic adenomas. Its sensitivity is reduced in small adenomas, multiglandular disease or associated multinodular goiter [4,18].

Concordance between ultrasound and scintigraphy allows minimally invasive focused parathyroidectomy. In case of discordant or negative results, second-line imaging is warranted before considering bilateral exploration [4,7].

6.3. Second-line imaging

Four-dimensional computed tomography (4D-CT) offers excellent spatial resolution and dynamic enhancement analysis, and is particularly useful in ectopic forms and reoperations, at the cost of non-negligible thyroid irradiation [18].

^{18}F -fluorocholine PET/CT is currently the most sensitive second-line modality, outperforming ultrasound and scintigraphy, especially for small or ectopic adenomas and in persistent or recurrent PHPT [18].

Cervicomediastinal magnetic resonance imaging is a non-irradiating alternative of more limited use.

6.4. Intraoperative tools

Intraoperative PTH measurement is an essential complement to focused surgery: a decrease of at least 50% from the pre-excision value, measured ten minutes after excision, predicts cure and avoids unnecessary bilateral exploration. In the absence of a sufficient decrease, exploration is extended to look for multiglandular disease [4,7].

Fine-needle aspiration with PTH measurement in the washout fluid may be useful in selected cases. By contrast, preoperative parathyroid biopsy should be avoided because of the risk of seeding and local fibrosis hampering subsequent surgery [7].

6.5. Genetic testing

Genetic counseling and molecular analysis (MEN1, RET, CDC73, CASR, GCM2) are recommended in the presence of young age at diagnosis, multiglandular disease, a family history of hypercalcemia or endocrine tumor, carcinoma or atypical adenoma, or recurrence after appropriate surgery [1,2,14].

7. Assessment of Severity

The assessment of severity aims to identify severe or complicated forms requiring urgent or priority management.

7.1. Acute hypercalcemic crisis

- **Definition:** serum calcium above 3.5 mmol/L (14 mg/dL), confirmed on two successive measurements.
- **Renal:** polyuria, polydipsia, severe dehydration, prerenal acute kidney injury.
- **Gastrointestinal:** nausea, vomiting, abdominal pain, constipation, paralytic ileus.
- **Neuropsychiatric:** agitation, confusion, lethargy, coma.
- **Cardiac:** QT shortening, arrhythmias and conduction disorders.
- **Causes:** parathyroid carcinoma, rapidly growing adenoma, or decompensation of chronic hypercalcemia triggered by dehydration.

This is a life-threatening emergency. Treatment combines abundant intravenous rehydration with isotonic saline, intravenous bisphosphonates, possibly calcitonin as an immediate bridge, calcimimetics in carcinoma-related forms, and surgery without delay once the patient is stabilized [5,9].

7.2. Severe skeletal involvement

- Osteitis fibrosa cystica, now rare, with diffuse bone pain, brown tumors and pathological fractures.
- Fragility fractures, including single or multiple morphometric vertebral fractures.
- T-score ≤ -2.5 at the lumbar spine, total hip, femoral neck or distal one-third radius in postmenopausal women and men aged 50 years and

older; Z-score ≤ -2.5 in premenopausal women and men younger than 50 years [1].

7.3. Severe renal involvement

- Nephrolithiasis, symptomatic or silent, and nephrocalcinosis.
- Estimated glomerular filtration rate below 60 mL/min/1.73 m².
- 24-hour urinary calcium above 250 mg/day in women and 300 mg/day in men. This threshold was lowered in 2022; it was previously set at 400 mg/day regardless of sex [1].

7.4. Cardiovascular involvement

More controversially, PHPT has been associated with persistent hypertension, left ventricular hypertrophy and vascular and valvular calcifications. These features are not among the validated surgical criteria, but they contribute to the overall risk assessment and may weigh in the decision in a borderline patient [1,3].

8. Differential Diagnosis

In practice, the differential diagnosis of PHPT follows two distinct axes: hypercalcemia, and isolated PTH elevation. The first step is to interpret PTH in light of serum calcium.

8.1. Hypercalcemia with elevated or inappropriate PTH

This is the setting of PHPT, but two diagnoses must be formally excluded.

Familial hypocalciuric hypercalcemia (FHH). It is due to an inactivating mutation of the CaSR or, more rarely, of the GNA11 and AP2S1 genes. It presents as mild, chronic, usually asymptomatic hypercalcemia discovered incidentally, with normal or slightly elevated PTH. The differential diagnosis is based on urinary calcium: unlike PHPT, 24-hour urinary calcium is low and, above all, the calcium/creatinine clearance ratio is below 0.01, whereas it is above 0.02 in PHPT. This calculation must be performed systematically before any surgical indication, as surgery is useless and does not improve hypercalcemia in FHH. Confirmation is genetic. Management is limited to monitoring and family counseling [1,8,9].

Drug-induced causes. Lithium decreases CaSR sensitivity and causes hypercalcemia with normal or elevated PTH, sometimes associated with true parathyroid hyperplasia. Thiazide diuretics increase tubular calcium reabsorption and may unmask or worsen hypercalcemia. When possible, these drugs should be discontinued and measurements repeated later [2,9].

Finally, PHPT must be distinguished from tertiary hyperparathyroidism, which develops after long-standing secondary hyperparathyroidism, mainly in patients with chronic kidney disease or kidney transplant

recipients, and is characterized by autonomous secretion with progression to hypercalcemia.

8.2. Hypercalcemia with suppressed PTH

A suppressed PTH points to non-parathyroid hypercalcemia.

- **Malignancy-associated hypercalcemia** is the first cause to consider. It results from secretion of PTH-related peptide (PTHrP) by solid tumors (lung, kidney, breast, head and neck), metastatic osteolysis, or production of 1,25-dihydroxyvitamin D by some lymphomas. Hypercalcemia is often severe and of rapid onset, in an obvious tumor context [17].
- **Granulomatous diseases:** sarcoidosis, tuberculosis and other granulomatous disorders, through unregulated extrarenal calcitriol production.
- **Vitamin D or vitamin A intoxication**, and milk-alkali syndrome.
- **Endocrine and miscellaneous causes:** hyperthyroidism, acute adrenal insufficiency, prolonged immobilization.

8.3. Elevated PTH without hypercalcemia

This is the most challenging situation, since it is where the diagnosis of normocalcemic PHPT is discussed. This diagnosis can only be made by exclusion, after ruling out all causes of secondary hyperparathyroidism [1,13]:

- **Vitamin D deficiency:** the most frequent cause; PTH can only be interpreted after normalization of 25-hydroxyvitamin D;
- **Chronic kidney disease:** nephron loss causes phosphate retention and impaired calcitriol synthesis, leading to hypocalcemia and chronic parathyroid stimulation;
- **Malabsorption:** celiac disease, inflammatory bowel disease, bariatric surgery, exocrine pancreatic insufficiency;
- **Idiopathic renal hypercalciuria**, to be investigated by 24-hour urinary calcium;
- **Drug-induced causes:** loop diuretics, bisphosphonates, denosumab, anticonvulsants.

The diagnosis of normocalcemic PHPT therefore requires repeatedly normal albumin-corrected total calcium and ionized calcium, sufficient 25-hydroxyvitamin D, preserved glomerular filtration rate and the absence of the other causes listed above [1,13].

9. Treatment

The goals of treatment are to normalize serum calcium, prevent skeletal and renal complications and improve quality of life.

9.1. General principles

Surgery is the reference treatment: parathyroidectomy is the only curative option. Medical therapy is reserved for patients who are not surgical

candidates or who decline surgery; it controls some parameters but does not cure the disease [5,6].

The strategy is based on three elements: the presence or absence of symptoms, target-organ involvement (skeletal, renal) and biochemical severity.

9.2. Parathyroidectomy

Parathyroidectomy is indicated in all symptomatic forms, and in asymptomatic forms meeting international criteria.

- **Focused parathyroidectomy** guided by concordant preoperative imaging, combined with intraoperative PTH measurement.
- **Bilateral neck exploration** in case of negative or discordant imaging, suspected multiglandular disease or familial forms.
- In diffuse hyperplasia: subtotal parathyroidectomy (resection of three and a half glands) or total parathyroidectomy with autotransplantation.
- In carcinoma: en bloc resection including the gland, its capsule and the ipsilateral thyroid lobe, without capsular rupture.
The cure rate exceeds 95% in experienced hands, surgeon volume being a recognized determinant of outcome [4,7].

9.3. Surgical indications (Fifth International Workshop, 2022)

Surgery is indicated in the presence of [1,5,7]:

- **Clinical symptoms:** symptomatic nephrolithiasis, fragility fracture, osteitis fibrosa cystica, hypercalcemic crisis;
- **Serum calcium** more than 0.25 mmol/L (1 mg/dL) above the upper limit of normal;
- **Skeletal involvement:** T-score ≤ -2.5 at the lumbar spine, total hip, femoral neck or distal one-third radius, or documented vertebral fracture, including morphometric fracture;
- **Renal involvement:** estimated glomerular filtration rate below 60 mL/min/1.73 m², 24-hour urinary calcium above 250 mg/day in women or 300 mg/day in men, nephrolithiasis or nephrocalcinosis, including silent forms;
- **Age below 50 years**, even in the absence of any other abnormality.

Two changes compared with previous recommendations deserve emphasis: the urinary calcium threshold, lowered from 400 mg/day to 250 mg/day in women and 300 mg/day in men, and the explicit recognition of silent involvement morphometric vertebral fracture, radiologically detected kidney stone as stand-alone surgical criteria. Outside these criteria, parathyroidectomy remains a legitimate option after informing the patient and obtaining consent [1].

9.4. Postoperative course

Transient postoperative hypocalcemia, usually mild and asymptomatic, is common and is managed with oral calcium and active vitamin D supplementation.

True hungry bone syndrome is, by contrast, rare in today's paucisymptomatic forms. It occurs mainly in severe high-turnover PHPT osteitis fibrosa cystica, large adenoma, very high PTH, elevated alkaline phosphatase and is characterized by profound and prolonged hypocalcemia with hypophosphatemia and hypomagnesemia, requiring intravenous and then high-dose oral calcium supplementation, sometimes for several months [19].

Other complications are rare (less than 2%): recurrent laryngeal nerve palsy, compressive neck hematoma, permanent hypoparathyroidism [4,7].

9.5. Medical treatment

Medical treatment is intended for patients who are not surgical candidates or who decline surgery, and never replaces surveillance.

- **General measures:** adequate hydration, normal dietary calcium intake restriction is harmful as it stimulates PTH —, and correction of vitamin D deficiency, which can be carried out under monitoring without significantly worsening hypercalcemia [5,8].
- **Bisphosphonates:** alendronate improves bone mineral density at the spine and hip, without effect on serum calcium or PTH. They are indicated in non-operated patients with osteoporosis [5,6].
- **Denosumab:** an alternative to bisphosphonates, particularly in renal impairment, with close monitoring of serum calcium at initiation.
- **Cinacalcet:** an allosteric CaSR agonist that normalizes serum calcium in most patients and modestly reduces PTH, but **does not improve bone mineral density**. It is indicated in case of surgical contraindication, refusal of surgery, severe hypercalcemia or parathyroid carcinoma. The most frequent adverse effects are nausea and hypocalcemia [5,6,20,21].
- **Cinacalcet–bisphosphonate or cinacalcet–denosumab combinations** may be considered when both serum calcium and bone density need to be addressed.
- **Hormonal therapies** (estrogens, raloxifene) have a modest effect on bone mineral density in postmenopausal women and are rarely used in practice given their benefit–risk ratio.

9.6. Follow-up of non-operated patients

• **Laboratory tests:** annual serum calcium and creatinine; PTH and 25-hydroxyvitamin D according to the clinical context.

• **Bone densitometry** at three sites, including the radius, every one to two years, with vertebral imaging in case of height loss or clinical suspicion.

• **Renal assessment:** renal imaging and stone work-up in case of clinical or biochemical suspicion. Any new surgical criterion arising during follow-up should prompt reconsideration of surgery [1,5].

10. CONCLUSION

Primary hyperparathyroidism is a common endocrinopathy, most cases of which are now diagnosed at an asymptomatic stage owing to routine serum calcium measurement and osteoporosis work-up. Classical forms osteitis fibrosa cystica, severe nephrolithiasis have become rare, but the disease remains associated with significant skeletal, renal and cardiovascular complications.

The diagnosis remains exclusively biochemical. Parathyroid imaging is used only in preparation for surgery, and negative imaging rules out neither the diagnosis nor the operation. "Asymptomatic" must not be equated with the absence of organ involvement: systematic assessment of the skeleton and kidneys is precisely what allows some of these patients to be reclassified and referred for surgery.

Parathyroidectomy remains the reference treatment, with an excellent prognosis when the indication follows international criteria. Medical therapies are alternatives for patients who are inoperable or decline surgery, but do not provide a cure.

The recommendations of the Fifth International Workshop (2022) introduced two major changes: a clarified definition of the three disease entities, and a lower urinary calcium threshold as a surgical criterion. They emphasize personalized risk stratification and close follow-up of non-operated patients. Correction of vitamin D deficiency is also essential so as not to underestimate disease severity.

Management of PHPT should therefore be multidisciplinary, involving rheumatologists, endocrinologists, nephrologists and specialized surgeons, in order to optimize clinical outcomes and prevent long-term complications.

Declarations

Conflict of interest: The authors declare no conflict of interest.

Funding: This work received no specific funding.

Author contributions: SZ conceived the review, performed the literature search and drafted the manuscript; ZB contributed to the literature review; AM and AB supervised the work and critically revised the manuscript. All authors approved the final version.

Use of artificial intelligence: A generative AI tool was used to assist with English translation and language editing; the authors reviewed all content and take full responsibility for the manuscript.

REFERENCES

1. Bilezikian JP, Khan AA, Silverberg SJ, *et al.*, Evaluation and management of primary hyperparathyroidism: summary statement and guidelines from the Fifth International Workshop. *J Bone Miner Res.* 2022;37(11):2293-2314.
2. Minisola S, Arnold A, Belaya Z, *et al.*, Epidemiology, pathophysiology, and genetics of primary hyperparathyroidism. *J Bone Miner Res.* 2022;37(11):2315-2329.
3. El-Hajj Fuleihan G, Chakhtoura M, Cipriani C, *et al.*, Classical and nonclassical manifestations of primary hyperparathyroidism. *J Bone Miner Res.* 2022;37(11):2330-2350.
4. Perrier N, Lang BH, Farias LCB, *et al.*, Surgical aspects of primary hyperparathyroidism. *J Bone Miner Res.* 2022;37(11):2373-2390.
5. Bilezikian JP, Silverberg SJ, Bandeira F, *et al.*, Management of primary hyperparathyroidism. *J Bone Miner Res.* 2022;37(11):2391-2403.
6. Ye Z, Silverberg SJ, Sreekanta A, *et al.*, The efficacy and safety of medical and surgical therapy in patients with primary hyperparathyroidism: a systematic review and meta-analysis of randomized controlled trials. *J Bone Miner Res.* 2022;37(11):2351-2372.
7. Wilhelm SM, Wang TS, Ruan DT, *et al.*, The American Association of Endocrine Surgeons guidelines for definitive management of primary hyperparathyroidism. *JAMA Surg.* 2016;151(10):959-968.
8. Khan AA, Hanley DA, Rizzoli R, *et al.*, Primary hyperparathyroidism: review and recommendations on evaluation, diagnosis, and management. A Canadian and international consensus. *Osteoporos Int.* 2017;28(1):1-19.
9. Walker MD, Silverberg SJ. Primary hyperparathyroidism. *Nat Rev Endocrinol.* 2018;14(2):115-125.
10. Bilezikian JP, Bandeira L, Khan A, Cusano NE. Hyperparathyroidism. *Lancet.* 2018;391(10116):168-178.
11. Marcocci C, Cetani F. Clinical practice. Primary hyperparathyroidism. *N Engl J Med.* 2011;365(25):2389-2397.
12. Yeh MW, Ituarte PHG, Zhou HC, *et al.*, Incidence and prevalence of primary hyperparathyroidism in a racially mixed population. *J Clin Endocrinol Metab.* 2013;98(3):1122-1129.
13. Cusano NE, Silverberg SJ, Bilezikian JP. Normocalcemic primary hyperparathyroidism. *J Clin Densitom.* 2013;16(1):33-39.
14. Thakker RV, Newey PJ, Walls GV, *et al.*, Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). *J Clin Endocrinol Metab.* 2012;97(9):2990-3011.
15. Pappu R, Jabbour SA, Reginato AM, Reginato AJ. Musculoskeletal manifestations of primary hyperparathyroidism. *Clin Rheumatol.* 2016;35(12):3081-3087.
16. Jones AC, Chuck AJ, Arie EA, Green DJ, Doherty M. Diseases associated with calcium pyrophosphate deposition disease. *Semin Arthritis Rheum.* 1992;22(3):188-202.
17. Zagzag J, Hu MI, Fisher SB, Perrier ND. Hypercalcemia and cancer: differential diagnosis and treatment. *CA Cancer J Clin.* 2018;68(5):377-386.
18. Patel DD, Bhattacharjee S, Pandey AK, *et al.*, Comparison of 4D computed tomography and F-18 fluorocholine PET for localisation of parathyroid lesions in primary hyperparathyroidism: a systematic review and meta-analysis. *Clin Endocrinol (Oxf).* 2023;99(3):262-271.
19. Witteveen JE, van Thiel S, Romijn JA, Hamdy NAT. Hungry bone syndrome: still a challenge in the post-operative management of primary hyperparathyroidism: a systematic review of the literature. *Eur J Endocrinol.* 2013;168(3):R45-R53.
20. Peacock M, Bilezikian JP, Klassen PS, Guo MD, Turner SA, Shoback D. Cinacalcet hydrochloride maintains long-term normocalcemia in patients with primary hyperparathyroidism. *J Clin Endocrinol Metab.* 2005;90(1):135-141.
21. Khan A, Bilezikian J, Bone H, *et al.*, Cinacalcet normalizes serum calcium in a double-blind randomized, placebo-controlled study in patients with primary hyperparathyroidism with contraindications to surgery. *Eur J Endocrinol.* 2015;172(5):527-535.
22. Bilezikian JP. Primary hyperparathyroidism. *J Clin Endocrinol Metab.* 2018;103(11):3993-4004.
23. Rosenthal AK, Ryan LM. Calcium pyrophosphate deposition disease. *N Engl J Med.* 2016;374(26):2575-2584.