

Primary Hyperparathyroidism: Review on Pathogenesis, Diagnosis, and Management

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ABSTRACT

Primary hyperparathyroidism is described as hypercalcemia due to excessive or inappropriate parathyroid hormone secretion caused by the over activity of one or more parathyroid glands. The sporadic type accounts for most primary hyperparathyroidism cases (90-95%), while familial hereditary accounts for only 5-10%.

Most primary hyperparathyroidism patients are asymptomatic, and their disease is discovered through incidental hypercalcemia findings. On the other hand, some patients may have Normocalcemia, a condition known as "Normocalcemic primary hyperparathyroidism." In contrast, others may have a normal parathyroid hormone level, indicating an inappropriate response to hypercalcemia.

This review focuses on sporadic classic primary hyperparathyroidism, including epidemiology, pathophysiology, preoperative workup, and treatment.

Key words: Hypercalcemia, Parathyroid hormone, Primary hyperparathyroidism

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INTRODUCTION

Primary hyperparathyroidism (PHPT) was discovered in the United States and Europe in 1920, and Felix Mandl performed the first parathyroid surgery in a patient with osteitis fibrosa cystica in Vienna in 1925. Albright described the Hypercalcemic state caused by PHPT five years later as a bone and stone disease [1-3].

PHPT is caused by parathyroid hormone (PTH) over-secretion in one or more parathyroid glands, which leads to hypercalcemia. Furthermore, it is considered the most common cause of hypercalcemia in ambulatory settings and is usually detected incidentally [4].

With estimated 0.1-0.4% prevalence, PHPT is the third most common endocrine disorder. Its prevalence rises with age and is highest in women between the ages of 50 and 60 [5].

It is divided into two types: sporadic (90-95%) and familial hereditary (5-10%). Solitary adenoma accounts for 85% of the causes in the sporadic type, followed by multiglandular parathyroid hyperplasia (10%) [2,6]. In the case of symptomatic PHPT, surgical intervention is recommended [2].

EPIDEMIOLOGY AND CAUSES

PHPT accounts for the third most common endocrine disease, with an estimated 0.1-0.4% prevalence. PHPT is considered the most common cause of hypercalcemia in ambulatory settings. Its incidence increases with age with a female predilection aged between 50 and 60 years [5].

Most cases are diagnosed in the asymptomatic phase in the United States, Europe, Canada, Germany, and Brazil. In contrast, renal and bone diseases are more common in some Asian countries, such as Saudi Arabia, India, Thailand, Iran, and Pakistan, than in other parts of the world [1,4,7].

The widespread adoption of routine serum calcium measurement was established in 1970. This is attributed to the detection of "asymptomatic PHPT," and subsequently, the incidence has increased. After 1998, there was another increase, possibly due to the establishment of osteoporosis screening guidelines [8].

PHPT is classified as either sporadic (90-95%) or familial hereditary (5-10%). In the sporadic type, solitary adenoma is the most prevalent cause (85%), followed by multiglandular parathyroid hyperplasia (10%). Other uncommon causes include double adenomas and parathyroid carcinoma (2-5%, < 1%, respectively). On the other hand, the familial hereditary type usually is caused by multiglandular parathyroid hyperplasia and multiple adenomas. Furthermore, the familial hereditary type is linked to some diseases, including multiple endocrine neoplasia type 1 and type 2A syndromes,

hyperparathyroidism-jaw tumor syndrome, and isolated familial hyperparathyroidism. Radiation exposure and drugs (such as lithium) have also been identified as risk factors for PHPT [2,4,6,9].

Pathophysiology

Typically, 99% of the calcium in the body is stored in the bone, with the remaining 1% in extracellular fluid. Vitamin D and PTH regulate serum calcium and keep it within the normal range (8.5-10.5 mg/dL [2.12-2.62 mmol/L]). Physiologically, PTH increases bone resorption, increases renal reabsorption of calcium, and inhibits renal reabsorption of phosphate. Furthermore, it promotes the synthesis of the active form of Vitamin D (1,25-dihydroxyvitamin D₃ [1,25(OH)₂D₃]), which increases calcium and phosphate absorption in the intestine. On the other hand, Vitamin D stimulates the release of calcium from the bone [2,6,10]. This regularity control is essential to ensure calcium's vital functions, including skeleton formation, muscle contraction, blood coagulation, and transmission of nerve impulses [4,11].

Physiologically, the calcium-sensing receptor on the chief cells detects small changes in serum calcium. As a result, high calcium levels block PTH production because of a negative feedback mechanism. A decrease in ionized calcium, on the other hand, causes PTH production [2,11]. In PHPT, the feedback mechanism is disrupted, and parathyroid activity is abnormal, resulting in excessive or inappropriate PTH production. Subsequently, renal absorption of calcium, synthesis of 1,25(OH)₂D₃, and bone resorption will increase in tandem with phosphaturia [2,4].

Presentation

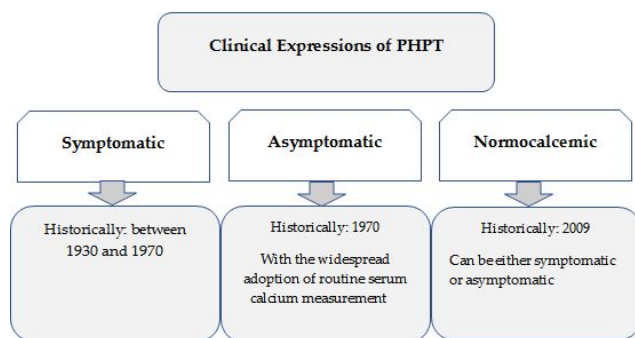


Figure 1: Clinical Expressions of PHPT [12].

The majority of PHPT patients (70-80%) are asymptomatic, and their disease is discovered through incidental findings of hypercalcemia [2]. PHPT typically affects the kidney and the skeleton. Other systems, such as the gastrointestinal, cardiovascular, and nervous systems, may also be affected as well [13] (Figure 1).

Musculoskeletal

The causes of musculoskeletal manifestations are due to hypercalcemia and the catabolic effect of PTH on cortical bones. The patients may exhibit muscle weakness, myalgia, bone pain, osteoporosis, osteopenia, bone cysts,

fractures, Brown's tumors, or osteitis fibrosa cystica (OFC) [3, 4]. The latter, which is the most severe complication of bone disease, is described as subperiosteal erosion in the radial aspect of the middle phalanx of the middle and ring fingers and tiny punched out lesions in the skull. In contrast to OFC, which is rarely seen nowadays, osteoporosis and osteopenia are the most common bone diseases seen in PHPT [3]. Moreover, OFC is associated with muscle weakness, which usually affects the proximal part. This weakness is caused by the atrophy of type II muscle fibers [6]. Interestingly, bone loss is often slowed or improved following PTx. Additionally, bone density increases over time [2].

Renal

PHPT can cause nephrolithiasis, nephrocalcinosis, renal colic, polyuria, and renal failure. Renal stones typically made up of calcium oxalate and calcium phosphate, are seen in 20-30% of patients. The presence of stones in the urinary tract can cause infection or obstruction. Hypercalciuria occurs when calcium exceeds the capacity of the renal tubules and is seen in 40% of patients. The term "nephrocalcinosis" refers to the diffuse deposition of calcium-phosphate complexes in the parenchyma. It causes phosphate retention, which significantly reduces urinary system functions [4,13].

Nephrolithiasis in symptomatic, asymptomatic, or normocalcemic PHPT patients mandates PTx [14]. It is observed that PTx reduces 24-hour urinary calcium excretion in most patients with PHPT and returns to normocalciuria in 79% of patients who had hypercalciuria at baseline [15].

Gastrointestinal

Patients with PHPT may experience abdominal pain, nausea, vomiting, pancreatitis, peptic ulcer, or constipation [10]. The latter is the most common symptom, affecting 30% of patients. Hypergastrinemia and a decrease in neuromuscular excitability both cause pancreatitis and peptic ulcers [4].

Neuropsychiatric

The presentation of psychological and neurological manifestations is common. Various studies have reported such symptoms as depression, lethargy, impaired concentration, dementia, memory loss, anxiety, confusion, or coma. Although the presence of neuropsychiatric manifestations is not a part of the indication for surgery in patients with PHPT, it has been found that these symptoms frequently improve after PTx [3].

Cardiovascular

The cardiovascular manifestations of PHPT are being debated. However, different studies have reported manifestations including hypertension, atherosclerosis, myocardial and valvular calcification, endothelial dysfunction, left ventricular hypertrophy, shortened Q-T

interval, bradycardia, heart block, arrhythmias, coronary artery diseases, and lipid abnormalities [16-18].

Hypercalcemia associated with severe PHPT (calcium \geq 11.2 mg/dl) has been linked to an increased risk of cardiovascular mortality (16, 18). Although the cardiovascular risk is not part of the indication for surgical intervention in patients with mild PHPT, PTx has been shown to improve cardiovascular morbidity and mortality. This improvement is not fully understood [19].

PHPT patients typically have elevated calcium and PTH levels. Conversely, the PTH level is significantly suppressed in non-parathyroid causes of hypercalcemia [1,5]. Moreover, some patients may have normocalcemia, a condition known as "Normocalcemic primary hyperparathyroidism (NPHPT)," while others may have a normal PTH level, indicating an inappropriate response to hypercalcemia [20].

Vitamin D levels should be checked in all PHPT patients because they can affect the interpretation of the PTH assay, and patients who have vitamin D deficiency should be replaced before PHPT is diagnosed [2,21].

Normocalcemic primary hyperparathyroidism (NPHPT)

While some authors described NPHPT as an early pattern of PHPT [1,5,12], others defined it as the unique

phenotype of the disease [22].

NPHPT has a prevalence ranging from 0.4 to 3.1%. In NPHPT, the serum albumin-corrected calcium and ionized calcium levels are persistently normal in the presence of high PTH level.

Furthermore, renal function, vitamin D level, and urinary calcium excretion are all within normal limits. These findings distinguish NPHPT from other secondary causes of high parathyroid hormone, such as vitamin D deficiency.

In three years of follow-up, it was reported that 19% of NPHPT patients developed hypercalcemia [1,5,12].

Diagnosis

PHPT diagnosis is based on biochemical laboratory tests (Table 1) rather than radiological features [10].

Classically, the majority of PHPT patients are asymptomatic and are diagnosed as a result of incidental hypercalcemia findings [10].

The differential diagnosis of hypercalcemia is shown in Table 2 [11].

Table 1: Biochemical Laboratory tests [4,11].

| | |
|-------------------------------|--------------------------------|
| Calcium | Elevated corrected calcium |
| PTH | High or Inappropriately Normal |
| Alkaline phosphatase | Normal or High |
| Phosphorous | Low |
| 24 hrs. urinary Calcium | High |
| Urinary calcium to creatinine | > 0.01 |

Table 2: Differential diagnosis of hypercalcemia (Reproduced with permission from Alqahtani et al. with minor changes (11)).

| |
|--|
| Primary hyperparathyroidism |
| Malignancy (Multiple myeloma, bone metastasis from breast and prostate cancer) |
| Increased oral calcium intake |
| Prolonged immobilization |
| Hyperthyroidism |
| Drugs (lithium, thiazides) |
| Milk-alkali syndrome |
| Hypervitaminosis D |
| Sarcoidosis |
| Familial hypocalciuric hypercalcemia |

Preoperative localization

Preoperative localization studies will serve to localize the adenoma and, as a result, guide the type of surgery,

namely minimally invasive parathyroidectomy (MIP) [23]. MIP is becoming the standard surgical technique for treating PHPT, with lower complication rates than

traditional bilateral neck exploration. In addition, MIP can be done under locoregional anesthesia and sedation, with small incisions [24].

There are two types of preoperative localization methods: invasive and non-invasive. Non-invasive methods include neck ultrasound, four-dimensional computed tomography (4D-CT), ^{99m}Tc-sestamibi scintigraphy, single-photon emission computed tomography (SPECT), magnetic resonance imaging (MRI), and positron emission tomography combined with CT scan (PET/ CT). Fine needle aspiration (FNA), selective venous sampling, and selective arteriography are invasive methods that are useful in re-operative cases [25].

The most common preoperative localization imaging techniques used in PHPT are US and ^{99m}Tc-sestamibi scintigraphy. When combined, the sensitivity rises to 90% [26], and in other reports, it reaches 95% [10]. A meta-analysis study found that US and sestamibi-SPECT are equally effective in preoperative localization of abnormal parathyroid glands in the case of PHPT. Furthermore, the authors concluded that 4D-CT improves accuracy [24].

Ultrasound (US)

The US is a simple, inexpensive, and effective method for detecting enlarged cervical parathyroid glands. Another advantage of the US is that it can be done both pre-and intra-operatively and has no risk of radiation exposure. Furthermore, it can evaluate the thyroid gland, as it has been reported that 18% of PHPT patients have synchronous thyroid disorders (2), and in another study, it ranged from 20% to 30% [22].

The US has a sensitivity of 70.4 % to 81.4%. Moreover, its positive predictive value ranging from 90.7% to 95.3% [27]. However, it has limitations in locating a parathyroid adenoma in the retro esophageal region, tracheoesophageal groove, intra-thyroidal, mediastinum, or other ectopic locations [28]. Furthermore, it is less effective in cases of multinodular goiter [10] and lesions smaller than 5mm [3].

One of the US pitfalls is that thyroid nodules and cervical lymph nodes can frequently be mistaken for parathyroid glands, so combinations with other modalities are recommended [29].

^{99m}Tc-sestamibi

In this radiological study, images are taken at 15 minutes and then after 2 hours after injection of the radiotracer.

The images show the focus of the radiotracer, indicating hyperfunctioning parathyroid [2].

The combination of SPECT with ^{99m}Tc-sestamibi scanning improves the sensitivity of localization for solitary adenomas by up to 87% and can distinguish parathyroid from thyroid tissue [10].

In contrast, sensitivity decreases in cases of double adenomas (30%) and multigland disease (44%) [2].

4D-CT

4D-CT is more sensitive than the US and provides a better view of the mediastinum. It is mainly used in re-operative cases when the initial ^{99m}Tc-sestamibi study is negative. It has a sensitivity and specificity of 60-80% and 85-98%, respectively [13]. Unfortunately, 4D-CT exposes patients to more radiation (>50 times more than ^{99m}Tc-sestamibi alone) [22] and cannot distinguish parathyroid glands from lymph node tissue [13].

Key points

US, ^{99m}Tc-sestamibi, and SPECT/CT have a higher sensitivity for detecting parathyroid adenoma than parathyroid hyperplasia.

Tc-99m and SPECT/CT are more helpful in detecting parathyroid adenoma, and an early SPECT/CT scan is preferable to a delayed one. Furthermore, compared to Tc-99m and SPECT/CT, the US is slightly better at localizing parathyroid hyperplasia. As a result, combining US with Tc-99m or SPECT/CT as the first modality in the localization of parathyroid hyperplasia is recommended [30].

Although MRI is rarely used, it is beneficial in patients with recurrent or persistent PHPT [29].

According to a systematic review, choline PET/CT is a promising technique for detecting hyper functioning parathyroid glands in PHPT patients [31].

In conservatively treated patients, bone density should be done as a baseline for regular monitoring [32]. The renal US is useful to confirm the presence of nephrolithiasis or nephrocalcinosis [32].

Management

Symptomatic PHPT, as well as asymptomatic patients who meet any one of the guidelines of the Fourth International Workshop on Asymptomatic PHPT, should be treated surgically (Table 3) [33].

Table 3: Indications of surgery for asymptomatic patients.

| |
|--|
| Serum calcium concentration of 1.0 mg/dL (0.25 mmol/L) or more above the upper limit of normal |
| Skeletal indications |
| BMD by DXA: T-score <-2.5 at the lumbar spine, total hip, femoral neck, or distal 1/3 radius. |
| Vertebral fracture (by radiograph, CT, MRI, or vertebral fracture assessment). |
| Renal indications |
| Creatinine clearance <60 mL/min. |

Twenty-four-hour urinary calcium >400 mg/day (>10 mmol/day) and increased stone risk by biochemical stone risk analysis

Nephrolithiasis or nephrocalcinosis by radiograph, ultrasound, or CT.

Age: younger than 50 years.

Surgical approaches for PTx include bilateral neck exploration and minimally invasive Para thyroidectomy (MIP). The former is the standard procedure and has several advantages, including improved inspection of all parathyroid glands, reduced morbidity, and prompt management of various presentations such as hyperplasia, supernumerary glands, double adenomas, and ectopic glands. MIP, on the other hand, employs a variety of techniques such as robotic, radio-guided, video-assisted, endoscopic, and focused lateral mini-incision [32].

Intraoperative PTH (IOPTH) monitoring is an important adjunct, particularly in MIP. Within 10 minutes of removing the diseased parathyroid gland or glands, the IOPTH level should drop by at least 50% into the normal range [1]. It has been reported that for inexperienced hands, the cure rate reached 95% [27] and in other reports, up to 98% [1].

Patients with asymptomatic PHPT who do not meet the criteria for surgical intervention and high-risk surgical candidates can be monitored for disease progression. This includes measurement of serum calcium, serum creatinine level, and estimated glomerular filtration rate annually. Furthermore, bone density (hip, spine, and forearm) should be measured every one to two years [22]. If there is a history of nephrolithiasis or a prevalent renal stone, annual abdominal imaging (radiography, US, or CT) and a 24-hour urine biochemical profile are recommended [27]. Again, asymptomatic patients who do not meet the criteria may choose PTx because it is the only definitive therapy available [1]. In NPHPT, both symptomatic and asymptomatic patients who meet the criteria should have surgery [1].

Advantages of PTx (reproduced with permission from Alqahtani et al. [11]).

Improve hypercalcemia symptoms.

Decrease the risk of nephrolithiasis.

Improve BMD.

Reduce the chance of bone fracture.

CONCLUSION

PHPT is the third most common endocrine disease and is considered the most common cause of hypercalcemia in ambulatory settings. Most of PHPT patients are asymptomatic, and their disease is discovered through incidental findings of hypercalcemia. In symptomatic PHPT, Para thyroidectomy is recommended.

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