



## Mini Review

# Primary hyperparathyroidism

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## Abstract

Primary hyperparathyroidism (PHPT) is an endocrinological disease with parathormone (PTH) and calcium elevation. It is the most common form of hypercalcemia in the community. In this review, the definition, diagnosis, differential diagnosis and treatment of hyperparathyroidism are described.

## Introduction

PHPT is characterized by increased PTH release from one or more parathyroid glands. It causes hypercalcemia. This hypercalcemia also leads to osteoporosis, bone fracture, urinary stone, kidney failure and adversely affects many systems. It is one of the most common endocrine diseases [1]. After 1970s, serum calcium entered the routine of measurement and the diagnosis of mild and / or symptomatic PHPT began to increase, not only symptomatic and severe PHPTs [2]. Nowadays, it presents in 3 ways:

1. Classic PHPT: condition with symptoms and signs specific to disease with high PTH and calcium [3].
2. Normocalcemic PHPT: Clinical form where total and ionized calcium levels are normal when PTH is high [3]. In order to make this sub-diagnosis, the level of vitamin D should be normal (> 20 ng/ml) and the other causes of secondary hyperparathyroidism (malabsorption, chronic kidney disease, hypercalciuria) should be excluded. Since vitamin D deficiency may mask hypercalcemia, hyperparathyroidism secondary to vitamin D deficiency should not be incorrectly called normocalcemic PHPT. After vitamin D replacement, the actual subtype of PHPT can be detected [2].
3. Asymptomatic PHPT: High PTH and calcium are not accompanied by clinical findings [3].

## Pathophysiology

Increased PTH acts on bone, kidney and small intestine. PTH directly stimulates osteoblasts, they release osteoclast-stimulating factors such as interleukin-6, thereby osteoclast activity increases. Increased osteoclast activity suppresses bone formation, increases resorption, thereby leading to bone loss and hypercalcemia. PTH causes an increase in calcium reabsorption and phosphorus excretion with direct effect on the kidneys and induces active vitamin D (1,25 dihydroxyvitamin) production by increasing the activity of 1 alpha hydroxylase enzyme, active vitamin D leads to an increase in calcium absorption from the small intestine. As a result, there is an increase in the level of calcium in the blood [4,5].

## Etiology

Primary hyperparathyroidism is the third most common endocrinological disease in the community after diabetes and thyroid diseases [6]. Its prevalence is about 1%. It is most commonly seen between the ages of 50–60. It is 3 times more common in women than in men, especially more common in postmenopausal women [7]. Since the 1970s, the prevalence of both PHPT and asymptomatic and mild PHPT has increased, with routine maintenance of serum calcium, widespread neck ultrasonography and osteoporosis screening. Asymptomatic PHPT rates of up to 80% are reported in some series. Especially in the USA and Europe, the diagnosis of mild / asymptomatic PHPT is more common than the obvious PHPT [8].

PHPT is usually sporadic, about 90% of which are solitary adenoma. 5%-10% of PHPT is due to multigland disease (multiple adenomas or hyperplasia), 1-3 % is caused by parathyroid carcinoma [7,8].

Approximately 10% of PHPT patients have a hereditary mutation. These mutations are mostly related to multiple endocrine neoplasia (MEN) type 1 (menin gene mutation on 11q13), MEN 2A (RET gene mutation on 10q11.1), familial isolated primary hyperparathyroidism (menin, parafibromin, CASR, CDKN1A, CDKN2B or CDKN2C mutations), hyperparathyroidism-jaw tumor syndrome (parafibromin gene mutation on 1q31.2) [9]. Its incidence is 13-36 in 100000 patient years in women and 66 in men. It is about 4 times more common in women [8]. (In which patients genetic testing is required, the diagnosis section is mentioned below).

### Clinical symptoms and signs

In symptomatic PHPT, symptoms / signs can develop in almost any system:

**Urinary system:** polyuria, polydipsia, nephrolithiasis, nephrocalcinosis. PTH leads to an increase in calcium reabsorption and phosphorus excretion in the kidneys. In PHPT, when the filter calcium load exceeds its absorption capacity, it leads to hypercalciuria, which starts the formation of stones and calcinosis.

**Gastrointestinal tract:** nausea, vomiting, acute pancreatitis, peptic ulcer. Peptic ulcer is generally seen in syndromic patients, especially in MEN1 and MEN4 because the frequency of gastrin-related tumors has increased in these syndromes. Whether there is a causal relationship between PHPT and acute pancreatitis has not been established yet.

**Musculoskeletal system:** weakness, bone pain, osteopenia / osteoporosis, brown tumor (osteitis fibrosa cystica). Chronic PTH elevation, through receptor activator of nuclear factor- $\kappa$ B ligand (RANKL), particularly affects distal radius, leading to bone loss, osteoporosis and pathological fractures. Osteitis fibrosa cystica occurs in 6.1% of patients. Recently, it is a less common bone complication characterized by bone loss, fibrosis and bone cyst.

**Cardiovascular system:** hypertension, arrhythmia, left ventricular hyperplasia. These findings are more common with PTH and calcium elevation. In asymptomatic / mild disease, the opposite is the case.

**Neuropsychiatric system:** depression, anxiety, concentration defect, stupor, coma. These findings are more common in correlation with high calcium and PTH, and low vitamin D, but there was no improvement in all after successful treatment [4].

### Diagnosis

Laboratory is very helpful in diagnosis. Serum calcium is normal / high, phosphorus is low / normal, PTH is close to normal upper limit / high, 25 hydroxi(OH) vitamin D is low

/ normal (due to an increase in 25 (OH) vitamin D clearance under the influence of 1 alpha hydroxylation). There are mild hyperchloremic acidosis, increase in bone alkaline phosphatase and urinary calcium excretion (> 400 mg / day). Calcium / creatinine clearance rate is > 0.01. Depending on the severity of the disease, the glomerular filtration rate may decrease [10].

In classical PHPT, hypercalcemia, hypophosphatemia and PTH are above the upper normal limit and clinical symptoms / signs are detected. If calcium is high, PTH is not suppressed, it is in favor of PHPT. However, today there is an increase in the frequency of mild symptomatic / asymptomatic PHPT and normocalcemic PHPT. Normocalcemic PHPT is a diagnosis made to rule out secondary causes of hyperparathyroidism. It is considered as the early stage of the disease, and if the diagnosis is delayed, it turns into an obvious disease. Secondary causes of hyperparathyroidism are discussed in the differential diagnosis section [4].

Although it is not necessary for the diagnosis, performing localization studies in people who meet the surgical criteria will make surgery easier. Lesions on the neck can be detected by the neck USG, imaging methods such as <sup>99m</sup>Tc-methoxyisobutylisonitrile (MIBI) scintigraphy + single-photon emission computed tomography (CT), CT, magnetic resonance (MR), positron emission tomography (PET)/CT can be used in mediastinal or ectopic lesions [1].

Nephrolithiasis and / or nephrocalcinosis can be detected by direct radiography, urinary USG or other imaging methods. Bone mineral density is determined with dual X ray absorptiometry (DXA) or quantitative CT (QCT) [11].

**Genetics:** Genetic testing should be considered in the presence of young age (<45 years), multiglandular disease (> 2 gland), first degree relative hypercalcaemia, parathyroid carcinoma, atypical adenoma [8]. In atypical adenoma, there are at least two of these: tumor necrosis without missing invasion of the capsule, fibrous bands, trabecular growth, mitotic activity > 1/10 HPF, tumor necrosis without definitive vascular invasion [12]. Genetic screening enables the application of adequate treatment, detection of other associated tumors, detection of index cases, avoiding unnecessary stress by identifying healthy family members [9].

### Differential diagnosis

PHPT is a disease with normal / high calcium and normal / high PTH. In differential diagnosis, especially malignancy, familial hypocalciuric hypercalcemia (FHH), drugs and secondary HPT should be taken into consideration.

Hypercalcemia can be seen in many types of malignancy, especially solid organ tumors [13]. In malignancies, both the cancer's self clinic and hypercalcemia clinic are faster and more severe, calcium is higher, especially PTH is too low or undetectable, these make it easy to distinguish from PHPT [14].

FHH is an autosomal dominant inherited disease. It is characterized by mild hypercalcemia and normal / mildly high PTH. Low urinary calcium helps distinguish it from PHPT.



It occurs due to inactivating mutation in calcium sensing receptors in parathyroid glands and kidneys. In these cases, the family story is positive. Genetic diagnosis is possible. Since it does not require treatment, differential diagnosis with PHPT is mandatory [15,16].

Lithium can cause downstream in calcium sensing receptors, similar to FHH, leading to a picture with hypercalcemia and hypocalciuria. With the discontinuation of the drug, the picture returns in most patients. Thiazide diuretics may decrease urinary calcium excretion and cause mild hypercalcemia. Calcium level returns to normal following discontinuation of the drug [17,18].

Secondary hyperparathyroidism is an increase in PTH secretion from parathyroid glands due to a decrease in extracellular calcium level. When PTH is high, serum calcium or ionized calcium is low or at the low normal limit. It is seen in cases of malabsorption, vitamin D deficiency (<20 ng/ml), bariatric surgery, kidney failure, loop diuretics, pseudohyperparathyroidism (genetic resistance to PTH, hypocalcemia, elevated PTH), hungry bone syndrome, antiresorptive agents (bisphosphonate, denosumab) [4,19,20].

### Treatment and follow up

In patients with a diagnosis of PHPT, the necessity for surgery should first be decided for treatment. Surgical treatment is indicated if there is nephrolithiasis, low creatinine clearance (GFR) unexplained for other reasons, presence of hyperparathyroidic bone disease, signs of hypercalcemia and/or life-threatening attacks of hypercalcemia. Unless asymptomatic PHPT was treated, an increased risk of vertebral fracture and kidney stone was found. Thus asymptomatic patients should be screened for these complications (4). In asymptomatic PHPT, surgery is indicated if one of the following is present: age <50 years, serum calcium with 1 mg/dl above the upper limit, GFR is lower than 60 ml/minutes, vertebra, hip or distal radius T score <-2.5 in DXA, vertebral fracture, urinary calcium excretion > 400 mg / day, nephrolithiasis or nephrocalcinosis [21,22].

The standard surgical procedure is bilateral cervical exploration with a 95-98% cure rate. This method should be preferred in PHPTH associated with genetic syndrome or where the lesion location cannot be detected or multigland involvement. Minimally invasive parathyroidectomy can be selected in single adenoma operation if intraoperative PTH can be performed and the surgical team is experienced. In these cases, endoscopic methods may also be an option [22,23].

With experienced surgeon, complications are few. These are laryngeal nerve damage (<1%), symptomatic moderate postoperative hypocalcemia (15%-30%), hungry bone syndrome (HBS), wound complications, cervical hematoma. Mortality rate is low but it can be seen up to 10% in the elderly [22,24].

HBS is a complication after parathyroidectomy with a frequency of 13%. Impaired balance between bone

resorption-formation after surgery causes it. Hypocalcemia may be accompanied by elevated PTH. Risk factors include vitamin D deficiency, alkaline phosphatase elevation, large parathyroid lesion, parathyroid-matched thyroid surgery, prolonged surgery, advanced age. Some guidelines and studies suggest preoperative vitamin D replacement and the use of bisphosphonates to reduce HBS risk. These agents reduce bone demineralization [25,26].

Medical treatment indications in PHPT are: > 50 years of age, the patient is minimally symptomatic or asymptomatic, calcium is <1.0 mg / dl higher than the normal upper limit, has no surgical indication or the patient does not want surgery or the patient is not suitable for surgery. In these situations, patients are followed up by medical monitoring [11,22].

There is no need for calcium restriction in the diet. Abundant daily hydration is recommended. If vitamin D is low, it is recommended to be replaced. The risk of hypercalcemia is low. It provides a slight drop in PTH [27].

Antiresorptive agents (estrogen receptor-targeted drugs, bisphosphonates) can be used in the presence of osteopenia / osteoporosis, these drugs provide a slight drop in calcium. Treatment of bone loss caused by the disease is also provided [28,29].

Sinekalset, which is a calcimimetic agent, normalizes 80%-90% in serum calcium and provides an increase in phosphorus. Urinary calcium is reduced. It does not affect bone mineral density [27].

Patients who do not receive surgical or medical treatment should be followed up periodically, and should be applied without delay when treatment indication develops. Biochemical tests (serum calcium, creatinine, GFR) of these patients are recommended to be performed annually, BMD follow-up is performed once in 1 or 2 years [30-35].

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