Simplifying the Complexity of Primary Hyperparathyroidism

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ABSTRACT

Primary hyperparathyroidism (PHPT) is a common but complex endocrine disorder. Historically, many PHPT patients have been diagnosed only after a protracted period of manifesting significant signs and symptoms. However, today, PHPT is often found during routine serologic screening or evaluation for decreased bone mass. Knowledge of PHPT is essential to ensure appropriate patient evaluation and treatment and to prevent adverse outcomes of chronic, untreated disease. Elevated serum calcium with subsequent elevated parathyroid hormone levels usually brings the diagnosis to light. The diagnosis of PHPT can be challenging and medical management is available, but surgery is the only cure.

Keywords: fractures, hypercalcemia, hyperparathyroidism, parathyroid hormone, parathyroid surgery

INTRODUCTION

Patients with primary hyperparathyroidism (PHPT) have abnormally elevated calcium (Ca) and parathyroid hormone (PTH) levels with respect to each other. In the United States, PHPT is the most common cause of hypercalcemia encountered in ambulatory care.[1] About 100,000 patients are diagnosed annually, producing an annual US incidence of < 10 per 100,000 and prevalence of up to 1%.[2] Before middle adulthood, the prevalence of PHPT is similar in men and women but is more common after age 65. Postmenopausal women have the highest incidence of PHPT.[2]

PHPT can have significant, insidious effects on the body, most commonly increasing bone turnover and decreasing bone mineral density (BMD). Failure to correct bone abnormalities has a negative impact on fracture risk. Severe bone disease, known as osteitis fibrosa cystica (OFC), only occurs in < 3% of patients in the US.[3] PHPT affects the central nervous, cardiac, renal, and gastrointestinal systems, yet patients may present asymptomatically with elevated Ca and PTH levels. Abnormalities in serum Ca and PTH levels often provoke questions from providers regarding the best approach to diagnostic testing and management. Prompt diagnosis and appropriate treatment of patients with parathyroid abnormalities is critical to mitigate adverse outcomes from unrecognized, chronic disease.

Symptomatic patients with mild PHPT improve after parathyroidectomy.[1] However, management of patients with mild, asymptomatic PHPT can be challenging. Although medical management is an option for patients with PHPT, surgery is indicated for patients who meet surgical criteria and is the only cure. The benefit of parathyroidectomy on body mass index, lifestyle, and psychological function as compared with no surgery is that surgery is a cost-effective treatment with minimal risk for complication from a single procedure.[4]

PARATHYROID GLANDS

The parathyroid glands are pea-sized glands located behind the thyroid gland. Expected anatomic findings upon exploration of the neck reveal 4 parathyroid glands, but ectopic parathyroid glands can be found in the thyroid, high in the neck or carotid sheath, in the retroesophageal space, and within the thymus or mediastinum. Parathyroid glands produce PTH, also known as parathormone, or PTH-intact.

All parathyroid glands that hypersecrete PTH are enlarged, sometimes to the size of a lima bean or larger. The parathyroid glands maintain levels of Ca and phosphorus. Ca plays an active role in metabolic processes, nerve impulse conduction, muscle contraction, and the clotting cascade. The vast majority of Ca is in bone, but it is also found in cells and fluids. Protein-bound and ionized, or free, Ca is carried in the plasma.

When serum Ca levels fall, PTH is secreted and serum Ca increases through bone resorption, while Ca excretion from the distal tubule in the kidneys decreases. PTH secretion increases Ca absorption from the duodenum by increasing renal formation of 1,25-dihydroxycholecalciferol [1,25$(OH)_2$D], the active form of vitamin D, from 25-hydroxycholecalciferol, the inactive form of vitamin D.[5] Vitamin D–deficient patients have increased bone turnover, more clinically significant disease, low BMD measurements, and more frequent fractures. PTH is negatively correlated with vitamin D; the lower the vitamin D level, the higher the PTH.[6]

When elevated PTH stimulates the renal tubular reabsorption of Ca, hypercalcemia ensues. The increase of Ca in the glomerular filtrate causes hypercalciuria. Nephrolithiasis is a classic renal manifestation of PHPT, and providers should consider parathyroid disease as a cause of nephrolithiasis.[7] Based on a negative feedback loop, PTH secretion is decreased when Ca reaches normal levels. Hypercalcemia suppresses PTH secretion.

Excess PTH can cause cortical demineralization, and severe, chronic hyperparathyroidism can cause diffuse demineralization, pathologic fractures, and OFC.[3] Elevations in osteocalcin and alkaline phosphatase, which are biochemical markers of bone formation, are found in patients with OFC.[3] Physiologic changes in bone structure through PTH influenced osteoblast activity are related directly to disease duration. Osteoblasts transport proteins and initiate bone mineralization.[8] The osteoblasts induce osteoclastogenic cytokine RANKL (receptor activator of nuclear factor-κB ligand) and may not cause bone changes in early PHPT disease states.[2] As the disease progresses, morphologic changes occur in cortical bone as a result of increased PTH. Excess PTH thins cortical bone as a result of endosteal bone reabsorption, increasing periosteal apposition and bone diameter, which protects against risk of fractures.[9] Bone loss in PHPT is studied based on fracture epidemiology, measurement of the shape or form of bone tissue, and BMD data.[9] Early diagnosis and appropriate referral for treatment of PHPT can prevent irreversible bone damage.

DEFINITION

Hyperparathyroidism occurs when serum PTH levels are elevated relative to serum Ca levels. Although hyperparathyroidism is associated with abnormal Ca metabolism, 2%-5% of patients are asymptomatic.[1] The diagnosis may be made upon incidental finding of hypercalcemia during routine blood tests or when routine BMD testing is abnormal.

Mild PHPT includes patients who have normal Ca levels with elevated PTH or elevated Ca levels with an inappropriately normal or high-normal PTH.[1] The most common cause of PHPT is parathyroid adenoma, found in 80% of patients.[10] Parathyroid hyperplasia occurs in 20% of patients with PHPT. It is an exceedingly rare cause of PHPT and occurs in $< 1\%$ of patients.[1] What may challenge providers is when patients have normocalcemic primary hyperparathyroidism (NPHPT), as demonstrated by persistently high PTH levels, and normal Ca levels with no secondary causes of parathyroid disease.[11] To make the diagnosis of NPHPT, secondary causes of elevated PTH must be ruled out including: medication effects (see Table 1); a glomerular filtration rate of < 60 mL/min; liver disease; and vitamin D

Table 1. Causes of Hypercalcemia Due to Medications

Thiazide diuretics[a]
Lithium[a]
Excessive amounts of antacids containing calcium and alkali[a]
Excessive intake of vitamin A[a]
Excessive intake of vitamin D[a]
Canagliflozin, an sodium-glucose linked transporter (SGLT2) inhibitor[b]
Hormone therapy (estrogens, antiestrogens, androgens, progestins)[c]
Theophylline

[a] From Endres.[14]
[b] From Kaur and Winters.[23]
[c] From the University of Michigan.[24]