Journal of Clinical Densitometry: Assessment of Skeletal Health, vol. 16, no. 1, 60−63, 2013

1094-6950/16:60−63/$36.00
http://dx.doi.org/10.1016/j.jocd.2012.11.010

Original Article

Medical Management of Primary Hyperparathyroidism

*Aliya A. Khan**

McMaster University, Hamilton, Ontario, Canada

Abstract

Primary hyperparathyroidism (PHPT) is the most common cause of hypercalcemia in the outpatient population. It is diagnosed in most individuals in the Western world at an asymptomatic stage without signs or symptoms of parathyroid hormone (PTH) calcium excess. Nonspecific symptoms include weakness, malaise, fatigue, and possible mood disturbances, which may be present at the time of diagnosis. The diagnosis of PHPT is confirmed in the presence of hypercalcemia and a normal or elevated PTH level in the absence of conditions that mimic PHPT. Indications for surgery have recently been revised based on international consensus, and surgery is advised in the presence of significant hypercalcemia, impaired renal function, and osteoporosis and in individuals younger than 50 yr. The classical complications of PHPT are skeletal fragility, nephrolithiasis, and nephrocalcinosis. Surgery is always appropriate in an individual with confirmed PHPT after excluding conditions that can mimic PHPT and in the absence of contraindications. Individuals with asymptomatic PHPT not meeting the guidelines for surgery or those with contraindications for surgery may be followed and considered for medical management. For those at an increased risk of fragility fracture, antiresorptive therapy may be considered with close monitoring of biochemical data and bone densitometry. Targeted therapy with a calcimimetic agent may be of value in lowering serum calcium and PTH. There are currently no fracture data for the medical options available, and prospective randomized controlled trials are required to confirm the effects of medical therapy on fracture risk reduction in those with asymptomatic PHPT.

Key Words: Bisphosphonates; cinacalcet; estrogen; medical management; primary hyperparathyroidism; raloxifene.

Introduction

In primary hyperparathyroidism (PHPT), parathyroid hormone (PTH) secretion is abnormally regulated, thereby leading to hypercalcemia in the presence of elevated or nonsuppressed PTH level *(1)*. PHPT occurs because of a sporadic solitary adenoma in 85−90% of the cases. Multiglandular hyperplasia is present in approx 5−10% of the cases, and fortunately carcinoma is rare occurring in less than 1% of the cases *(1)*. PHPT can occur at any age; however, it is most commonly seen in the postmenopausal female population, and the prevalence is 1−4 per 1000 people *(1)*.

Accepted 11/18/12.
*Address correspondence to: Aliya A. Khan, MD, FRCPC, FACP, FACE, McMaster University, 209-331 Sheddon Avenue, Oakville, Ontario L6J 1X8, Canada. E-mail: aliya@mcmaster.ca

Calcium homeostasis is carefully regulated by 3 calcium-regulating hormones, namely PTH, 1,25-dihydroxy vitamin D, and calcitonin. A decrease in serum calcium is sensed by the calcium-sensing receptor (CASR) in the chief cells of the parathyroid glands and increases PTH synthesis and secretion. PTH increases distal renal tubular calcium reabsorption, stimulates osteoclast-mediated bone resorption, and increases the synthesis of 1,25-dihydroxyvitamin D in the proximal renal tubule. Increases in 1,25-dihydroxyvitamin D levels lead to enhanced intestinal absorption of calcium and phosphate as well as mobilization of calcium from the skeleton *(1)*. These 3 effects of PTH result in normalization of serum calcium. The release of fibroblast growth factor-23 is stimulated by 1,25-dihydroxyvitamin D and enhances renal phosphate losses, reduces the secretion of PTH, and inhibits the hydroxylation of 25-hydroxyvitamin D.

These homeostatic mechanisms lead to normalization of serum calcium within a few minutes to hours of the

hypocalcemic insult. Elevations in serum calcium lead to decreases in PTH synthesis and secretion and enhanced renal calcium losses, decreases in 1,25-dihydroxyvitamin D, and decreases in the release of calcium from the bone. Renal calcium losses are also enhanced by the direct effects of calcium on the CASR in the distal renal tubule. These effects result in normalization of serum calcium. The effects of PTH in normalizing serum calcium are illustrated in Fig. 1. Binding of calcium to the CASR in the chief cells of the parathyroid glands decreases the release of PTH (Fig. 2).

The medical management of PHPT has focused on inhibition of bone resorption by bisphosphonates or estrogen. These agents have not been able to normalize serum calcium as renal calcium reabsorption in the presence of excess PTH continues and reestablishes hypercalcemia, thereby maintaining serum calcium at the higher set point. Calcimimetic agents bind to the CASR and are effective in lowering serum PTH and calcium levels. To date, an effect on bone mineral density (BMD) or the biochemical markers of bone remodeling has not been observed with these agents.

Individuals with mild asymptomatic PHPT may be suitable for therapy with antiresorptive agents designed to provide skeletal protection and prevent progressive decreases in bone density. Calcimimetic agents may be effective in lowering serum calcium and PTH and may be of value in those with mild PHPT or individuals unable or unwilling to proceed with surgery. The third international workshop on the management of asymptomatic PHPT developed recommendations regarding who should proceed with parathyroidectomy and who can be safely monitored and considered for targeted medical intervention *(2)*. Recommendations for the diagnosis of PHPT and for the clinical presentation of asymptomatic PHPT were also published *(3–5)*. This article summarizes the medical options that may be offered to those with asymptomatic PHPT in order to provide skeletal protection or lower serum calcium and PTH.

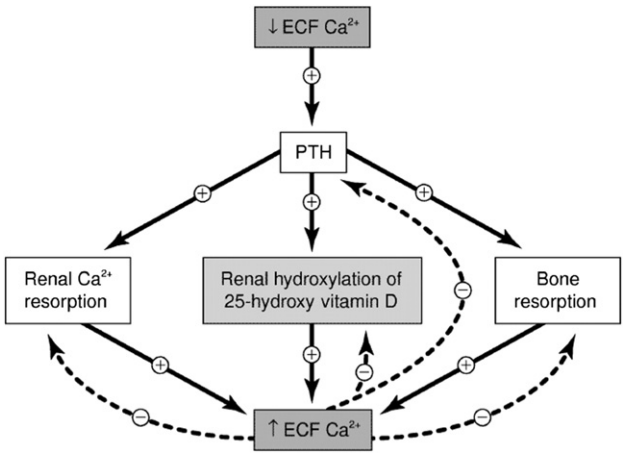

Fig. 1. Calcium homeostasis with regulation of serum calcium levels via feedback inhibition through the calcium receptor. ECF, extracellular; Ca, calcium; PTH, parathyroid hormone (Reprinted with permission from Khan A, Bilezikian J. 2000 Primary hyperparathyroidism: pathophysiology and impact on bone. CMAJ 163:184–187, Fig. 1, p185).

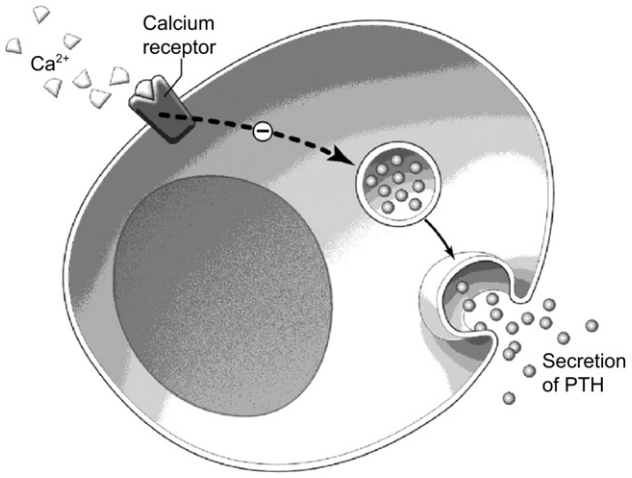

Fig. 2. Schematic illustration of calcium binding to the calcium receptor at the parathyroid cell and inhibiting PTH secretion. Ca, calcium; PTH, parathyroid hormone (Reprinted with permission from Khan A, Bilezikian J. 2000 Primary hyperparathyroidism: pathophysiology and impact on bone. CMAJ 163:184–187, Fig. 2, p185).

General Measures

It is necessary to ensure that individuals with symptomatic PHPT maintain adequate hydration and avoid volume contraction as this can exacerbate the hypercalcemia and contribute to the development of a hypercalcemic crisis. In the event of intercurrent illness leading to inadequate fluid intake or fluid losses, serum calcium should be checked and correction of volume status should be undertaken. Dietary calcium intake should not be limited, and patients may take 1000 mg elemental calcium from dietary sources on a daily basis. Vitamin D levels should be measured as this patient population has been found to have a higher prevalence of vitamin D inadequacy owing to elevations in PTH, thereby enhancing the conversion of 25-hydroxy vitamin D to 1,25-dihydroxy vitamin D. Vitamin D inadequacy can be associated with higher PTH levels after parathyroidectomy and a higher risk of hungry bone syndrome after surgery *(6,7)*. Correction of the vitamin D inadequacy has been a concern owing to fears of exacerbating the degree of hypercalcemia. It is recommended that gradual correction of vitamin D inadequacy be undertaken with close monitoring of serum and urine calcium and PTH levels *(2)*. Careful replacement of inadequacy should be undertaken. Grey et al *(8)* have demonstrated that cholecalciferol in doses of 50,000 IU/wk for 1 mo followed by monthly doses was effective in lowering PTH levels without leading to further increases in serum calcium. In this 12-mo study, PTH levels decreased by 26% in 21 patients with