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Original Article

Medical Management of Primary Hyperparathyroidism

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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)*.

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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.

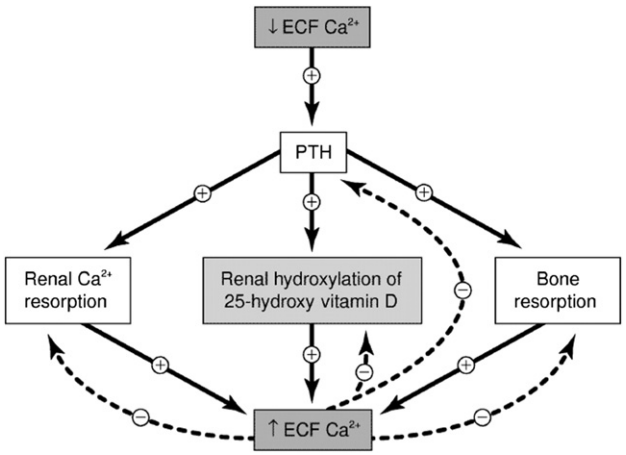

Fig. 1. Calcium homeostasis with regulation of serum calcium levels via feedback inhibition through the calcium receptor. ECF, extracellular; Ca, calcium; PTH, parathyroid hormone (Reprinted with permission from Khan A, Bilezikian J. 2000 Primary hyperparathyroidism: pathophysiology and impact on bone.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

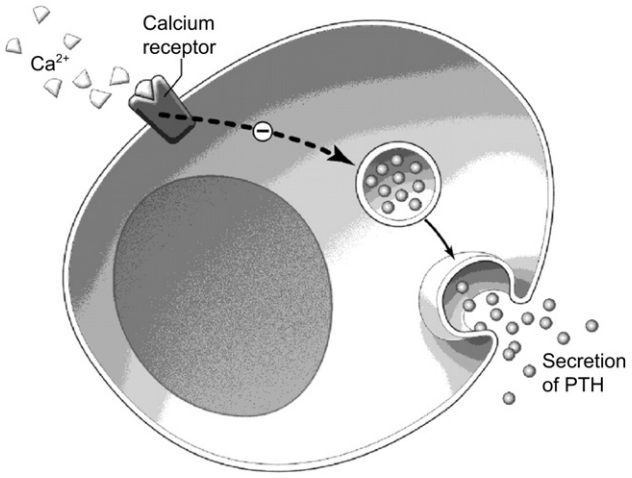

Fig. 2. Schematic illustration of calcium binding to the calcium receptor at the parathyroid cell and inhibiting PTH secretion. Ca, calcium; PTH, parathyroid hormone (Reprinted with permission from Khan A, Bilezikian J. 2000 Primary hyperparathyroidism: pathophysiology and impact on bone. CMAJ 163:184–187,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

PHPT. The vitamin D levels were less than 50 nmol/L at baseline *(8)*. None of these patients demonstrated increase in serum calcium levels. Two patients did develop increases in urine calcium. All the patients had baseline serum calcium levels lower than 3 mmol/L, and it remained under this value with vitamin D supplementation *(8)*. It is possible that vitamin D replacement prevents growth of parathyroid adenomas and further increase in PTH level. Ensuring that the concentration of 25-hydroxy vitamin D level is at or higher than 50 nmol/L is one of the recommendations from the international workshop on the management of PHPT *(9)*.

Certain drugs can further elevate serum calcium or mimic PHPT and should be discontinued if at all possible. Hydrochlorothiazide enhances renal calcium reabsorption and can further increase serum calcium. Lithium elevates the set point for calcium and can lead to elevations in both serum calcium and PTH. It may not be possible to stop lithium, and in these difficult situations close monitoring of serum calcium and PTH is recommended.

Aminobisphosphonates have been demonstrated to lower serum calcium in those with malignancy *(10)*, and its effectiveness in lowering serum calcium in PHPT has been extensively evaluated *(2)*. Pamidronate, the first aminobisphosphonate used in PHPT, was given in 30-mg doses intravenously to 10 patients and resulted in transient decreases in serum calcium level from 10.88 ± 0.24 to 9.96 ± 0.16 mg/dL (2.72 ± 0.06 to 2.49 ± 0.04 mmol/L) after 1 wk of administration *(11)*. During the treatment period, PTH levels did increase and the decrease in serum calcium was found to be transient *(11)*. Risedronate has also been evaluated in doses of 20 and 40 mg/d for 7 d and demonstrated decreases in serum calcium after 1 wk of administration *(12)*. Alendronate has been extensively investigated and has been shown to decrease bone turnover and increase BMD in those with PHPT *(13,14)*. In an international multicenter trial, 44 patients with PHPT were randomized to receive either alendronate 10 mg/d for 12 mo or placebo followed by an additional 12-mo crossover study of the placebo group to active alendronate therapy *(15)*. Over 2 yr of therapy, alendronate led to increases in the lumbar spine and total hip BMD in comparison with baseline. There were no significant changes at the distal one-third radius site. BMD was measured at the lumbar spine, femoral neck, total hip, and distal one-third radius site every 6 mo. Calcium, phosphorous, PTH, bone-specific alkaline phosphatase (BSAP), urinary calcium, and urinary *N*-telopeptide (NTX) excretion were monitored every 3 mo. Marked reductions in bone turnover markers were noted with decreases in urinary NTX excretion by 66% at 3 mo and decreases in BSAP by 49% at 6 mo ($p < 0.001$). In the placebo group, NTX and BSAP levels remained elevated. The serum calcium, both total and ionized, as well as PTH and urine calcium did not change with alendronate therapy at the time points measured *(15)*. In this study, there was no decrease in serum calcium observed with alendronate therapy, and this may have been owing to the presence of relatively well-maintained vitamin D levels in the study population. The mean 25-hydroxy vitamin D levels were 45.5 nmol/L at baseline. Other investigators have shown transient decreases in serum calcium with bisphosphonate therapy; however, the vitamin D levels were lower in these study populations and may have contributed to these findings *(14)*.

Estrogen in doses of 0.625 mg/d and medroxyprogesterone acetate 5 mg/d have been evaluated in 42 postmenopausal women with PHPT in comparison with placebo group *(16)*. The study demonstrated increases in BMD at the total body, lumbar spine, and femoral neck sites in those receiving estrogen replacement therapy. Bone turnover also significantly decreased, and ionized calcium and intact PTH levels remained stable *(16)*. Rubin et al *(17)* have evaluated raloxifene and its effects on PHPT and demonstrated decreases in the biomarkers in this short-term study. PTH, alkaline phosphatase, and urinary calcium levels were stable in this short-term study *(17)*. Bone loss has been prevented at the spine and the hip in 3 patients with PHPT as noted by Zanchetta et al *(18)*.

Calcimimetic agents increase the sensitivity of the CASR to extracellular calcium leading to lowering of synthesis and secretion of PTH and serum calcium. Cinacalcet is a calcimimetic agent, which has been evaluated in 78 patients with PHPT in a randomized placebo-controlled trial *(19)*. In this study, the primary endpoint was a predose serum calcium less than 2.57 mmol/L and a decrease 0.12 mmol/L or higher *(19)*. This endpoint was observed in 5% of those on placebo and 73% on cinacalcet. The cinacalcet-treated group also demonstrated increases in serum phosphorous with rises from 0.87 ± 0.16 to 1.03 ± 0.16 mmol/L ($p < 0.001$) *(19)*. There were no significant changes in the biochemical markers of bone remodeling or 1,25-dihydroxy vitamin D levels or the 24-h urinary calcium-to-creatinine ratio *(19)*. BMD also did not change significantly with cinacalcet therapy *(19)*. A total of 45 individuals were evaluated in a 4-yr open-label extension of this study. BMD remained stable, and serum calcium was maintained at a lower value throughout the 5-yr study period. Cinacalcet was well tolerated, and adverse events were essentially limited to nausea or headache *(20)*. Cinacalcet has also been shown to be effective in lowering serum calcium in those with parathyroid carcinoma *(21)*. The drug has now been approved for the management of PHPT and secondary hyperparathyroidism in many countries and is a valuable addition to the medical treatment options available for hyperparathyroidism. A short trial of cinacalcet can also be of value in assessing the potential benefits of parathyroidectomy in elderly individuals with cognitive impairment. The cognitive impairment may be owing to multiple factors, including hypercalcemia and an underlying dementia. If lowering of serum calcium is associated with improvements in cognition, then this may indicate a reversible component to the underlying cognitive impairment and may lead to consideration of parathyroidectomy in this patient population. Cinacalcet has not been shown to improve bone density or lower the biomarkers of bone remodeling. Its effect on fracture risk is currently not known.

New and emerging antiresorptive options include denosumab and odanacatib, and their effects on preserving bone density and bone strength need to be evaluated.

In conclusion, many advances have been made over the past decade in the diagnosis and the medical and surgical

management of PHPT. International consensus has been reached on who can be safely followed with medical management and close monitoring. Surgery is always an appropriate intervention; however, there are individuals with mild asymptomatic disease who may be closely followed and offered targeted medical intervention options in order to maintain skeletal health and or lower serum calcium level. There are no fracture data with the medical options available today. There are however valuable cohort data demonstrating reductions in fracture risk with surgery, and those individuals meeting the guidelines for surgical intervention should be considered for surgery at a center offering expertise in parathyroid surgery. In those individuals in whom medical monitoring is suitable, it is important to ensure adequate physical activity, maintenance of hydration, and appropriate vitamin D replacement. Antiresorptive therapy can provide skeletal protection, and cinacalcet has been demonstrated to lower serum calcium and PTH levels in those with mild-to-severe PHPT.

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