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*This article has been peer reviewed.*

CMAJ 2000;163(2):184-7

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# Primary hyperparathyroidism: pathophysiology and impact on bone

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## Abstract

Primary hyperparathyroidism has been associated with bone loss, especially at cortical skeletal sites. Results from studies evaluating the mineral density of cancellous bone have been more difficult to interpret. Most densitometry studies support the concept that the parathyroid hormone appears to be catabolic at cortical sites and may have anabolic effects at cancellous bone sites. Studies completed to date, however, have been limited by design, definitions of fracture and inadequate control groups. Primary hyperparathyroidism is now increasingly being detected during the asymptomatic phase. The need for parathyroidectomy has been questioned in such patients because there may be no disease progression in the absence of surgery. Medical management of primary hyperparathyroidism has to date been limited to estrogen replacement therapy in postmenopausal women. Identification of the calcium receptor has improved our understanding of calcium homeostasis, and significant reductions in calcium receptor levels have been detected in parathyroid adenomas. Thus, a new class of therapeutics may include the calcimimetic agents. Bisphosphonates are also currently being evaluated with regard to their impact on fracture prevention and their beneficial effects on bone mineral density.

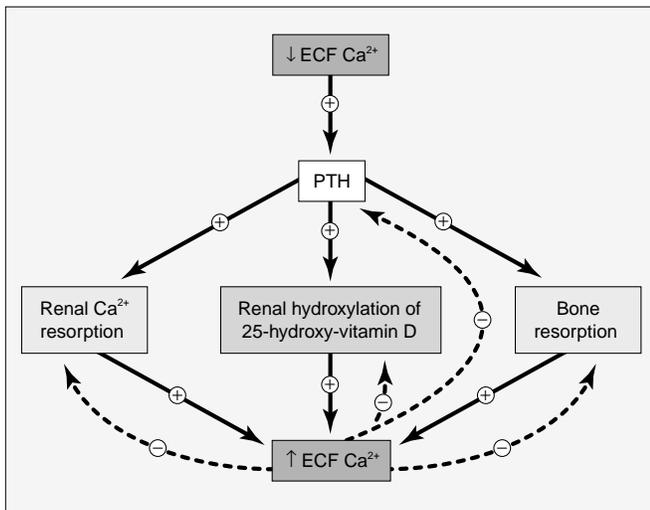
Primary hyperparathyroidism was previously characterized by severe hypercalcemia, recurrent nephrolithiasis, osteoporosis and osteitis fibrosa cystica (cystic bone destruction).<sup>1</sup> In the 1970s mild hypercalcemia became easily detectable with the introduction of the autoanalyser, and thus a 4-fold increase in the incidence of primary hyperparathyroidism was seen.<sup>2</sup> Most people are asymptomatic at the time of diagnosis. Recently a decline in the incidence of primary hyperparathyroidism has been reported.<sup>3</sup> With the limitation on screening that is now occurring in the United States and Canada, the incidence of primary hyperparathyroidism could decline further. Currently the prevalence rates are about 1 to 4 per 1000, with a female:male ratio of 3:1.<sup>4</sup> In Sweden about 3% of postmenopausal women are affected.<sup>5</sup>

This paper reviews the pathophysiology of primary hyperparathyroidism in the context of the current understanding of calcium homeostasis, the effect of primary hyperparathyroidism on bone mineral density, and advances in the clinical management of the disorder.

## Pathophysiology

Parathyroid hormone (PTH) secretion is normally stimulated by a fall in the extracellular calcium concentration. PTH subsequently increases renal calcium reabsorption in the cortical thick ascending limb. It stimulates the hydroxylation of 25-hydroxy-vitamin D at the proximal convoluted tubule in the kidney and increases bone resorption through stimulation of osteoclast-activating factors such as interleukin-6 from osteoblasts.<sup>6</sup> Through these actions PTH helps to restore any tendency to hypocalcemia (Fig. 1).

Current understanding of calcium homeostasis has been advanced by the discovery of the calcium receptor that allows calcium to act with PTH and 1,25-dihydroxy-vitamin D<sub>3</sub> in maintaining calcium homeostasis.<sup>7</sup> When extracellular calcium binds to the calcium receptor in the parathyroid cell, PTH secretion and parathyroid cell growth are inhibited (Fig. 2). At the kidney this interaction between calcium and the calcium receptor inhibits the 1-hydroxylation of 25-



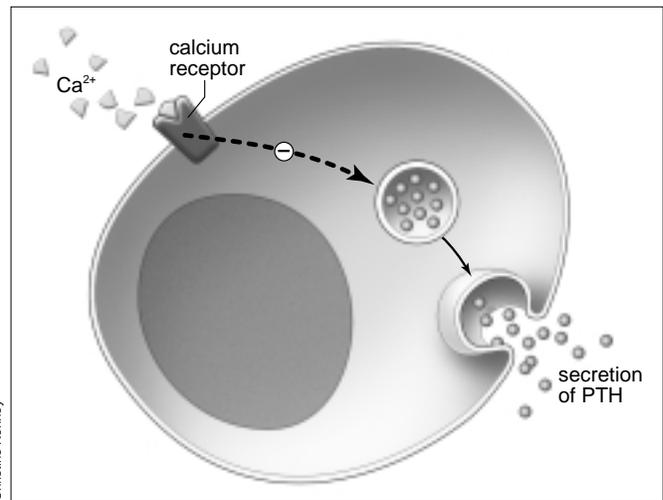
**Fig. 1: Calcium homeostasis with regulation of serum calcium levels via feedback inhibition through the calcium receptor.** ECF = extracellular, Ca = calcium, PTH = parathyroid hormone.

hydroxy-vitamin D. Calcium affects the thyroid C cells, stimulating calcitonin release, and in bone may potentially regulate bone resorption.<sup>8</sup>

The identification of 2 clinical conditions caused by mutations in the calcium receptor gene has confirmed the key role that the calcium receptor plays in calcium homeostasis.<sup>9,10</sup> The first condition is familial hypocalciuric hypercalcemia. Heterozygous inactivating mutations of the calcium receptor result in mild hypercalcemia and hypocalciuria. A relative resistance leads to a higher set point required for inhibition of PTH secretion by calcium, as well as impaired urinary calcium excretion. The renal defect persists following total parathyroidectomy. Levels of PTH tend to be normal or only slightly elevated in this condition.<sup>9</sup> The second condition is that of an autosomal dominant activating mutation of the calcium receptor.<sup>10</sup> In this condition the calcium receptor is abnormally sensitive to calcium, leading to suppression of PTH secretion at hypocalcemic levels. This is a form of hypoparathyroidism. Relative hypercalciuria also occurs.

In primary hyperparathyroidism mutations of the calcium receptor gene have not been identified. However, significant reductions in calcium receptor mRNA levels have been detected in parathyroid adenomas.<sup>11</sup> The pathophysiological significance of this observation is unclear because the reductions could be secondary to the chronic hypercalcemia and not the primary cause.

Up to 10% of cases of primary hyperparathyroidism are hereditary. These hereditary forms are due usually to multiple endocrine neoplasia I (MEN I) or to MEN II. Familial primary hyperparathyroidism in the absence of other endocrine disease also occurs. It has been shown recently that as many as 25%–30% of people with sporadic primary hyperparathyroidism can have abnormalities in the gene responsible for MEN I.<sup>12–14</sup>



**Fig. 2: Schematic illustration of calcium binding to the calcium receptor at the parathyroid cell and inhibiting PTH secretion.**

## Effect on bone

Primary hyperparathyroidism is associated with a reduction in bone mineral density. Older cross-sectional studies used single photon absorptiometry to assess density at the forearm. More recent studies have used dual energy x-ray absorptiometry to quantify bone mineral density at 3 sites: the lumbar spine, the hip and the forearm. It appears that primary hyperparathyroidism is associated with bone loss largely at cortical sites.<sup>15–17</sup>

Data evaluating the density of cancellous bone are more difficult to interpret. Some studies have shown a modest decrease at cancellous bone sites.<sup>18–21</sup> Other studies, however, indicate that bone density is relatively well preserved.<sup>17,22</sup>

The largest and longest study comes from Silverberg and colleagues,<sup>23</sup> who demonstrated stable bone mineral density in the majority of people with primary hyperparathyroidism in the absence of surgical intervention. One hundred and twenty-one people with a mean age of 55 years were followed prospectively over 10 years. Bone mineral density was stable in the majority of the patients, although a subgroup of about 25% showed a decrease in bone mineral density. This subgroup consisted of women who had entered menopause without estrogen supplementation, those with advanced primary hyperparathyroidism and those whose parathyroidectomy had failed. These findings support the need to monitor patients with primary hyperparathyroidism who are not planning to undergo parathyroid surgery.

These studies have shown that there may be differing responses to elevated PTH levels, depending on the skeletal site. Thus, most densitometry studies support the concept that PTH appears to be catabolic at cortical sites and may in fact have anabolic effects at cancellous bone sites. In some patients, however, cancellous bone density of the lumbar spine can be substantially reduced.<sup>24</sup>

A number of retrospective and case-control studies have not shown an increase in fracture incidence among patients with primary hyperparathyroidism,<sup>25-27</sup> whereas others have.<sup>28-30</sup> These studies are limited by their cross-sectional design, inadequate control groups, ascertainment biases and imprecise definitions of fracture. There clearly is a need for large prospective controlled studies to evaluate fracture incidence in primary hyperparathyroidism.

## Clinical management

### Surgical

The need for parathyroidectomy in patients with asymptomatic disease has been questioned. In 1990 the National Institutes of Health held a consensus development conference on asymptomatic primary hyperparathyroidism.<sup>31</sup> Guidelines for surgical intervention were developed, and it was agreed that people with mild disease who were asymptomatic could be followed safely with medical monitoring (Box 1). About half the patients with primary hyperparathyroidism will have 1 or more of these criteria for surgical intervention. Patient preference is also an important consideration in choosing the appropriate intervention. Localization tests include ultrasonography, computed tomography, magnetic resonance imaging and technetium-99m sestamibi scanning. Sestamibi scanning with computed tomography provides better resolution. Preoperative localization studies are indicated in those patients who have had prior neck surgery. They are not recommended routinely because the surgical success rate in experienced hands is better than in current imaging technology. After parathyroidectomy, increases in bone mineral density at the lumbar spine and femoral neck have been observed in a large prospective study.<sup>23</sup>

### Medical

Hormone replacement therapy in the management of primary hyperparathyroidism has been evaluated in several studies.<sup>18,32,33</sup> Conjugated equine estrogen, 0.625 mg/d, and medroxyprogesterone acetate, 5 mg/d, over 2 years were effective in improving bone mineral density in the lumbar spine (by  $5.2\% \pm 1.4\%$ ,  $p = 0.002$ ) and in the femoral neck (by  $3.4\% \pm 1.5\%$ ,  $p = 0.05$ ). Total body bone mineral density (bone mineral density measured over the entire skeleton) also increased (by  $1.3\% \pm 0.4\%$ ,  $p = 0.004$ ).<sup>32</sup> Increases at the proximal femur were also seen compared with baseline values.<sup>32</sup> These findings have been supported by those of other investigators.<sup>18,33,34</sup> Hormone replacement therapy appears to slow bone loss and increase bone mineral density in patients with primary hyperparathyroidism.

Bisphosphonates represent a potential alternative in the medical management of primary hyperparathyroidism. Clodronate has been evaluated in hyperparathyroidism,<sup>35-38</sup> and reductions in serum calcium levels have been documented accompanied by a significant decline in bone loss

#### Box 1: National Institutes of Health guidelines for parathyroidectomy<sup>31</sup>

- Serum calcium level > 3 mmol/L
- Unexplained decline of creatinine clearance by 30%
- Marked hypercalciuria with calcium level > 10 mmol in 24-hour urine collection
- Cortical bone mineral density > 2 standard deviations below the mean for age-matched control subjects
- Patient requests surgery
- Patient unable to be followed up for monitoring
- Age < 50 years

with decreases in urinary calcium and urinary hydroxyproline excretion.<sup>36</sup> No significant associated change in PTH levels has been noted.<sup>35</sup> Treatment for more than 3 months with clodronate has, however, been associated with a partial recurrence of hypercalcemia because of a compensatory rise in serum PTH levels.<sup>37,38</sup> The short-term effectiveness of risedronate has been evaluated in patients with primary hyperparathyroidism.<sup>31</sup> The serum calcium concentration was again found to decrease after drug therapy, and an associated compensatory increase in PTH levels was documented. Bone loss was inhibited, as shown by reductions in the fasting urinary hydroxyproline:creatinine ratio and the serum alkaline phosphatase level.<sup>37</sup> The bisphosphonate etidronate has been found to have little effect on serum calcium levels in primary hyperparathyroidism.<sup>39</sup>

Data regarding alendronate in primary hyperparathyroidism are limited to a few abstracts.<sup>40,41</sup> Patients treated with this drug have gained bone at the lumbar spine, hip and radius. Bone loss was evident at all sites except the lumbar spine in the untreated patients.<sup>40</sup> Alendronate is being evaluated further in primary hyperparathyroidism in studies that use a more rigorous experimental design.

Calcimimetic agents mimic the effect of calcium at the calcium receptor. One such agent is the phenylalkylamine compound R568, which has been shown in animal studies to be effective in decreasing cytoplasmic calcium levels, PTH secretion and serum calcium levels.<sup>42</sup> R568 has been shown to reduce PTH secretion and ionized calcium levels in 20 postmenopausal women with asymptomatic primary hyperparathyroidism.<sup>43</sup> Other calcimimetic agents are being evaluated in clinical trials and may become effective treatment options in the medical management of primary hyperparathyroidism.

## Conclusion

People with primary hyperparathyroidism that is mild and asymptomatic can be followed without surgical intervention, because most patients with asymptomatic disease who do not undergo surgery do not demonstrate disease

progression. Medical options are limited to estrogen therapy in postmenopausal women; the potential efficacy of bisphosphonates and calcimimetics remains to be demonstrated. Medical follow-up should include annual bone densitometry, with monitoring of both cancellous and cortical bone mass. If only one bone site is to be assessed it should be a site rich in cortical bone, preferably the distal one-third of the radius. Medical management has not been shown to affect adversely morbidity and mortality in people with asymptomatic hyperparathyroidism. When surgery has been deemed to be necessary, significant increases in bone mineral density at the lumbar spine and femoral neck have been documented after parathyroidectomy.

Competing interests: None declared.

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