Primary hyperparathyroidism: rheumatologic manifestations and bone disease

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INTRODUCTION AND HISTORY

The effects of parathyroid hormone (PTH) on its major target organs, the skeleton and the kidneys, gave rise to the original description of primary hyperparathyroidism more than 70 years ago as a disease of “bones, stones and groans.” The classic bone disease, osteitis fibrosa cystica, included degranulation of the skull (or “salt and pepper skull”), distal tapering of the clavicles, subperiosteal bone resorption (particularly in the phalanges), brown tumors, and bone cysts. In addition to these skeletal manifestations, rheumatologic manifestations of primary hyperparathyroidism were described commonly. Gout with elevated serum uric acid concentrations and pseudogout caused by CPPD crystal deposition in joints were appreciated as classic manifestations of primary hyperparathyroidism. Gout or pseudogout occasionally developed even after successful parathyroid surgery. Patients also periodically complained of non-specific arthralgia symptoms. A neuromuscular disorder with atrophy of type II muscle fibers was sometimes featured as a major manifestation of the disease. These aspects of primary hyperparathyroidism were consistent with the traditional idea that parathyroid hormone in excess can affect organ systems besides the skeleton and the kidneys.

Over the past 30 years, this traditional description of primary hyperparathyroidism has been replaced by a presentation that is primarily asymptomatic. The shift in the presentation from a symptomatic to an asymptomatic clinical phenotype has been due to the widespread use of the multichannel autoanalyzer that typically includes the serum calcium measurement.

CURRENT MODE OF PRESENTATION

Most patients with primary hyperparathyroidism are women in their postmenopausal years. The serum calcium concentration is typically within 1 mg/dL above the upper limit of normal, and the parathyroid hormone concentration is usually 1.5 times above the upper limit of normal. Hypercalcemia is seen in approximately 40% of patients. Hypophosphatemia, reflecting the physiologic actions of PTH to cause phosphaturia, is seen in less than 25% of patients. Overt hyperparathyroid bone disease with specific radiologic findings is vanishingly rare. The incidence of kidney stone disease has diminished to approximately 15% to 20% of all patients, although it remains the most common complication of primary hyperparathyroidism. Consistent with this modern presentation, patients rarely have overt neuromuscular disease but may still complain of vague muscle weakness and easy fatigability. Rheumatologic manifestations that can be ascribed specifically to the articular system, and which are reviewed here, are uncommon and have been relegated to case reports. These manifestations can be divided into the impact on crystal-related arthropathies (gout and pseudogout) and non-specific effects on bones and joints.

CRYSTAL ARTHROPATHIES

Gout

The incidence of gout appears to be increased in patients with primary hyperparathyroidism who have hyperuricemia. Rather dramatic radiologic manifestations can sometimes be seen, as in the case report of an individual who presented with a lytic lesion initially assumed to be a brown tumor but which was found on joint aspiration to contain urate deposits. A possible explanation for the association of gout and primary hyperparathyroidism is the increased levels of serum uric acid that have been described in some, but not all, cohorts of patients with primary hyperparathyroidism. Data on serum uric acid in primary hyperparathyroidism are limited. However, in one study, 53 subjects with primary hyperparathyroidism had significantly higher serum uric acid levels, along with a reduction in the clearance of uric acid as compared with age- and sex-matched control subjects. Within 6 months after successful parathyroid surgery in 26 subjects, serum uric acid levels declined significantly. It has been suggested that PTH might inhibit uric acid excretion in the proximal renal tubule. Pseudohypoparathyroidism, a disease associated with renal resistance to PTH, was found in one kindred to be associated with hypouricemia and an increase in the fractional excretion of uric acid, therefore suggesting an important role for PTH in the renal handling of urate.

Calcium pyrophosphate dihydrate crystal deposition disease (pseudogout)

Primary hyperparathyroidism and CPPD crystal deposition have been associated in numerous reports. As is the case for CPPD in general, aging confers greater risk for radiographic evidence of CPPD in primary hyperparathyroidism. Mechanisms other than chronic hypercalcemia might be particularly relevant to the process of CPPD crystal deposition in joints of subjects with primary hyperparathyroidism. It has been speculated that the function of proteoglycans that normally inhibit
calcium pyrophosphate crystallization might be impaired by elevated calcium levels in serum and in joint fluid. It has also been postulated more recently that hyperparathyroidism in patients with CPPD have abnormal local cartilage metabolism of pyrophosphate. The nucleoside triphosphate pyrophosphohydrolase (NTPPH) enzymes, which normally catalyze the production of pyrophosphate, appear to be overactive. Excess NTPPH activity could promote the formation and ultimate deposition of calcium- and pyrophosphate-containing material in the joints.

The episode of pseudogout after parathyroid surgery appears to be triggered by the fall in serum calcium. As the serum calcium falls, it is presumed that the synovial fluid calcium concentration also falls, rendering the pyrophosphate crystals more soluble and thus released into the synovial space. The idea that a rapid reduction in the serum calcium is primarily responsible for an attack of CPPD and not the primary hyperparathyroidism per se comes from other reports in which pseudogout has been precipitated after medical treatment that leads to hypocalcemia. One report describes a case of pseudogout in the setting of mithramycin treatment for hypercalcemia and another in the setting of hypocalcemia after alendronate treatment. Similarly, injection of the joint space with hyaluronate can precipitate pseudogout, possibly because the phosphate in the hyaluronate preparation may lower intra-articular calcium concentrations, leading to crystal shedding.

**PRIMARY HYPERPARATHYROIDISM AND THE SKELETON**

Evidence indicates that excess PTH may have an adverse effect on joints in addition to the specific situations mentioned earlier. These rheumatologic effects are consistent with the classic notion that PTH is catabolic at skeletal sites. However, our understanding of the skeletal effects of PTH has changed along with the evolving clinical profile of primary hyperparathyroidism. Thus in the series of Silverberg and colleagues, less than 2% of patients with primary hyperparathyroidism had specific skeletal manifestations of hyperparathyroidism by conventional x-ray examination. Along with the rarity of overt skeletal disease in primary hyperparathyroidism, other less common target organs of the primary hyperparathyroid state including the articular system have also become rare manifestations. The effects on the skeleton of mild primary hyperparathyroidism are therefore the key consequence to be considered.

**Skeletal effects of mild primary hyperparathyroidism**

With primary hyperparathyroidism now commonly presenting as an asymptomatic disorder, it has been possible to address a far more subtle but critically important question: Do patients with asymptomatic primary hyperparathyroidism have evidence for skeletal involvement? Using dual-energy x-ray absorptiometry (DXA), Silverberg and colleagues have provided evidence that in asymptomatic primary hyperparathyroidism, there is skeletal involvement, although this is site specific. Bone mineral density (BMD) is reduced at the distal third of the radius, a site that reflects mainly cortical bone. In the lumbar skeleton, enriched in cancellous bone, skeletal mass is relatively well preserved in patients with primary hyperparathyroidism with only small reductions from age- and sex-specific norms. Bone mineral density of the hip region, which contains a more even admixture of cortical and cancellous elements, is intermediate between cancellous and cortical sites (Fig. 200.1).

This pattern of bone loss in postmenopausal women with primary hyperparathyroidism differs from the usual pattern of the early postmenopausal years, when cancellous bone of the lumbar spine is lost preferentially. In estrogen-deficient postmenopausal women with primary hyperparathyroidism, bone density at the lumbar spine is generally well preserved, emphasizing a protective effect of PTH against the loss of cancellous bone (Fig. 200.2). On the other hand, although a pattern of selective cortical bone loss is most commonly seen in primary hyperparathyroidism, about 15% of patients will demonstrate substantial reductions in bone density at the lumbar spine.

These observations suggest that patients with primary hyperparathyroidism should not be at risk for fractures of the axial skeleton where bone mass is relatively well preserved, whereas they might be expected to show an increase in fracture incidence of the appendicular skeleton where bone mass is preferentially reduced. Unfortunately, few studies confirm this expectation and fracture data are conflicting.

**Parathyroid hormone therapy and joint manifestations**

It is also important to consider the rheumatologic consequences of “medical” hyperparathyroidism as a consequence of therapy with PTH. Teriparatide (recombinant human PTH 1-34, brand name Forteo) increases BMD and reduces fracture incidence in postmenopausal women with osteoporosis (Fig. 200.3). Teriparatide also increases BMD in men with primary or hypogonadal osteoporosis. In comparison to alendronate, it has a greater effect to reduce vertebral fractures in glucocorticoid-induced osteoporosis. As opposed to primary hyperparathyroidism, in which exposure to elevated PTH is continuous, once-daily administration of teriparatide stimulates new bone formation on trabecular and cortical surfaces by preferential stimulation of osteoblast activity. Although it is theoretically possible that adverse rheumatologic effects, formerly seen frequently in primary hyperparathyroidism, could be experienced in some PTH-treated patients, this has not been noted clinically. Clinical trials have shown that treatment with teriparatide resulted in 3% of patients with serum uric acid
DIAGNOSIS AND TREATMENT OF PRIMARY HYPERPARATHYROIDISM

The diagnosis of primary hyperparathyroidism is made on the basis of an elevated serum calcium concentration and a parathyroid hormone level that is either elevated or inappropriately normal. When the parathyroid hormone level is elevated in a patient with hypercalcemia, the differential diagnosis includes use of thiazide diuretics or lithium, familial hypocalciuric hypercalcemia, and the tertiary hyperparathyroidism associated with end-stage renal disease. Humoral hypercalcemia of malignancy should not be a consideration when the parathyroid hormone level is high because the hypercalcemic agent in this condition, parathyroid hormone-related protein, is not detected by the currently available immunoradiometric assays for parathyroid hormone.
SECTION 16  •  METABOLIC BONE DISEASE

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NEW VERTEBRAL FRACTURES

RR 0.38
(95% CI, 0.22 to 0.55)*

Risk reduction % 0 25 50 75 100

% of women 14

Placebo

TPTD20

No. of women who had >1 fracture

64

22

Placebo (n=448)  TPTD20 (n=444)

* P<0.001 vs. placebo

Fig. 200.3 Reduction in the risk of new morphometric vertebral fractures in postmenopausal women with severe osteoporosis afterPTH(1-34) 20 mg/day, over a median treatment period of 19 months, compared with placebo. (Reprinted with permission from Hodman AB, Bauer DC, Dempster DW, et al. Parathyroid hormone and teriparatide for the treatment of osteoporosis: a review of the evidence and suggested guidelines for its use. Endocr Rev 2005;26:688-703.)

Surgical treatment

Surgery is indicated in patients with overt symptoms of classic disease (i.e., kidney stones, osteitis fibrosa cystica). In patients with few if any symptoms, guidelines to aid clinical decision making are based on the Third International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism (Table 200.1). Patients who undergo successful parathyroidectomy show rapid normalization of serum calcium and PTH levels. Improvement in bone mineral density at the spine and hip follows over a 3- to 4-year period after surgery. Most patients who are asymptomatic and do not meet surgical criteria do well without evidence for progressive disease. However, approximately 37% of patients will experience progressive disease. Only age appears to be predictive of progression; patients younger than 50 years of age are approximately three times more likely to experience worsening disease, than patients older than age 50.

Medical treatment

Development of a medical approach to asymptomatic primary hyperparathyroidism has attracted considerable interest. The use of estrogen therapy in postmenopausal women with primary hyperparathyroidism is associated with small reductions in the serum calcium concentration and increases in bone density, along with stable parathyroid hormone levels. Raloxifene, a selective estrogen receptor modulator, is a potential alternative, with calcium-lowering effects similar to estrogen in postmenopausal women with primary hyperparathyroidism. Bisphosphonates have also been considered as a possible medical approach to primary hyperparathyroidism. Alendronate has been shown to increase lumbar spine bone mineral density in patients with primary hyperparathyroidism by approximately 4% to 6%. In most studies, serum calcium and parathyroid hormone levels do not change significantly. The calcimimetic drug cinacalcet HCl has been investigated in patients with primary hyperparathyroidism and was approved by the Food and Drug Administration for use in patients with secondary hyperparathyroidism on dialysis and in patients with parathyroid cancer. It has become available in Europe for the management of primary hyperparathyroidism. This drug binds to the calcium receptor on the surface plasma membrane of the cell and thus increases the affinity of this receptor for its cognate ligand, calcium. The subsequent increase in intracellular calcium leads to a reduction in parathyroid hormone synthesis and secretion. With this drug, patients with primary hyperparathyroidism have sustained normalization of serum calcium levels for up to 3 years. No improvement in bone density was noted in conjunction with the reduction in calcium.

CONCLUSION

In the past, symptomatic primary hyperparathyroidism was associated with abnormalities of the articular system. Now that primary hyperparathyroidism is generally asymptomatic in the United States and in most of the developed world, rheumatologic manifestations are mainly of historical interest only. Primary metabolic conditions such as PHP, although uncommon, should be considered in CPPD occurring before age 55 and can be considered in patients presenting after age 55. In patients who present with rheumatologic manifestations along with primary hyperparathyroidism, a search for other conditions should be undertaken before concluding that the patient might be unusually affected in this way by the hyperparathyroid state.

KEY REFERENCES

REFERENCES

Full references for this chapter can be found on www.expertconsult.com.