



BRIEF ANSWERS  
TO SPECIFIC  
CLINICAL  
QUESTIONS

## Q: How should I follow a patient with mildly elevated serum calcium and PTH, but no symptoms?

**JENNIFER WOJTOWICZ, DO**

Department of Endocrinology, The Cleveland Clinic

**CHRISTIAN NASR, MD**

Department of Endocrinology, The Cleveland Clinic

**A:** In patients with mildly elevated calcium (< 1 mg/dL above the upper limit for the laboratory) and parathyroid hormone (PTH), the first thought is asymptomatic primary hyperparathyroidism. To confirm the diagnosis check the following.

**The serum calcium concentration, corrected for albumin.** For every gram-per-decimeter reduction in the serum albumin concentration below 4.0 g/dL, the measured serum calcium concentration should be adjusted upward by 0.8 mg/dL.

**Ionized calcium** can also be measured but lacks standardization.

**The PTH concentration** should be obtained at the same time as the calcium.

**Twenty-four-hour urinary calcium excretion** should be measured to evaluate the calcium burden on the kidneys and to investigate for familial hypocalciuric hypercalcemia (FHH).

FHH is a rare disorder of the calcium-sensing receptor (CaSR) gene. It can present with mildly increased calcium and normal or mildly elevated PTH levels. However, 24-hour urinary calcium excretion is generally normal in FHH. Moreover, the ratio of calcium clearance to creatinine clearance (fractional excretion of calcium) is generally < 0.01 in FHH; in contrast, it is usually > 0.02 in primary hyperparathyroidism. Although FHH is rare, it is important to exclude it to avoid unnecessary parathyroid surgery.

### ■ WHEN IS SURGERY NECESSARY?

#### Look for subtle symptoms

Next, confirm that the patient truly has no symptoms. Besides the classic “moans, bones,

and abdominal groans,” which generally do not occur if the calcium concentration is only mildly elevated (< 1 mg/dL above the upper limit of normal for the laboratory), look for more subtle problems, eg:

**Mild cognitive changes** (especially in the elderly)

#### Worsening hypertension

**Osteoporosis or osteopenia.** One should obtain bone densitometry scans of the lumbar spine, femoral neck, and distal radius, looking at cortical and trabecular bone. In elderly patients already at risk for osteoporosis, it is difficult to confirm whether bone loss is related to hyperparathyroidism alone. However, if bone loss is accelerated or the z score (which is age-matched) is low, then hyperparathyroidism is more likely to be the cause. Another clue that hyperparathyroidism is the cause is if the forearm bone loss is out of proportion to trabecular bone loss, since endogenous PTH is thought to be catabolic at cortical sites.

**Kidney stones.** Abdominal radiography or ultrasonography can be done to look for renal calculi, especially if there is an unclear history of urolithiasis. The sensitivity of abdominal radiography is about 50%, and its sensitivity is about 75%.

It is difficult to predict whether asymptomatic mild elevations of serum calcium will progress to symptomatic or complicated disease. Silverberg et al<sup>1</sup> followed 52 patients for 10 years, and the disease progressed to the point that it required surgery in only 14 (27%). However, patients with a history of kidney stones were more likely to have recurrent stones if they did not have surgery.

In 1991, the National Institutes of Health published a consensus statement on the diagnosis and management of asymptomatic primary hyperparathyroidism.<sup>2</sup> The consensus

**It is hard  
to predict who  
will progress  
to symptomatic  
or complicated  
disease**

**TABLE 1****Indications for surgery in asymptomatic hyperparathyroidism: 2002 consensus recommendations**

Any of the following:

- Serum calcium > 1 mg/dL above accepted range  
(changed from 1–1.6 mg/dL above accepted range in the 1991 report)
- 24-hour urinary calcium excretion > 400 mg
- Creatinine clearance reduced by 30% compared with age-matched normal subjects
- Bone mineral density T score < –2.5 at any site  
(changed from a forearm Z score < –2.0 in the 1991 report)
- Age < 50 years
- Coexisting disease complicating management
- Unable to have consistent follow-up

BASED ON BILEZIKIAN JP, POTTS JT JR, FULEIHAN GH, ET AL. SUMMARY STATEMENT FROM A WORKSHOP ON ASYMPTOMATIC PRIMARY HYPERPARATHYROIDISM: A PERSPECTIVE FOR THE 21ST CENTURY. J CLIN ENDOCRINOL METAB 2002; 87:5353–5361.

**Follow up  
patients with  
asymptomatic  
hyperpara-  
thyroidism  
every 6 months**

panel recommended that patients with only mild elevations in calcium and stable renal and bone status be monitored, without parathyroid surgery. The committee reconvened in 2002 because more patients were being diagnosed with relatively asymptomatic disease, owing to increased screening.<sup>3</sup> **TABLE 1** shows the indications for surgery in the old and the new consensus documents.

#### ■ FOLLOW-UP CARE

The new consensus statement also outlines the follow-up care of patients with asymptomatic hyperparathyroidism.

Hydration needs to be maintained, especially during illness or surgery, to prevent kidney stones. Accordingly, diuretics should be avoided.

Follow-up visits should be twice a year and should include evaluation of symptoms and serum calcium. Serum creatinine levels and bone density should be measured once a year. If the baseline 24-hour urinary calcium excretion was elevated, this measurement should be repeated annually. If there is a change in the serum creatinine level, then creatinine clearance should be reevaluated.

Patients who have normal serum levels of 1,25-dihydroxyvitamin D should maintain a normal level of calcium intake (1,200 mg/day). Patients with elevated 1,25-dihy-

droxyvitamin D levels have a greater risk of hypercalciuria if dietary calcium is increased; however, a diet very low in calcium is generally not beneficial since it can lead to further stimulation of PTH. Additionally, a low serum 25-hydroxyvitamin D level (< 20 ng/mL) can stimulate PTH secretion. A physiologic dose of vitamin D (400–600 IU/day) is recommended with monitoring of calcium.

The new consensus panel leaves open the question of how long to continue follow-up. Continued biannual monitoring of serum calcium is prudent. If there is no change in bone mineral density after 2 years, then monitoring every 2 years is reasonable.

#### Medical treatment of primary hyperparathyroidism

**Estrogen replacement therapy** slows bone loss and increases bone mineral density.

**Raloxifene** has been shown to lower serum calcium levels by 0.6 mg/dL and to reduce markers of bone resorption in postmenopausal women with primary hyperparathyroidism. It did not reduce PTH levels, however.<sup>4</sup>

**Bisphosphonates** decrease bone loss, but PTH levels can increase in response to lowering of serum calcium levels.<sup>5</sup> However, more recent studies have shown no significant elevations in PTH with use of bisphosphonates in patients with primary hyperparathyroidism.





17. **Shrader E, for the Study Group.** Equivalence of St. John's wort extract (ZE 117) and fluoxetine. *Int Clin Psychopharmacol* 2000; 15:61–68.
  18. **Stevinson C, Ernst E.** Hypericum for depression. An update of the clinical evidence. *Eur Neuropsychopharmacol* 1999; 9:501–505.
  19. **Lecrubier Y, Clerc G, Didi R, Kieser M.** Efficacy of St. John's wort extract WS 5570 in major depression: a double-blind, placebo-controlled trial. *Am J Psychiatry* 2002; 159:1361–1366.
  20. **St. John's wort.** In: Physicians Desk Reference for Herbal Medicines 2000. Medical Economics Company, 2000:719–725.
  21. **Markowitz JS, Donovan JL, DeVane L, et al.** Effect of St. John's wort on drug metabolism by induction of cytochrome P450 3A4 enzyme. *JAMA* 2003; 290:1500–1504.
  22. **McGuffin M, editor.** Botanical Safety Handbook. Boca Raton, Fla: CRC Press, Inc., 1997:62–63.
  23. **Mathijssen R, Verweij J, de Bruijn P, Loos WJ, Sparreboom A.** Effects of St. John's wort on irinotecan metabolism. *J Natl Cancer Inst* 2002; 94:1247–1249.
  24. **Mansky P, Straus S.** St. John's wort: more complications for cancer patients (editorial). *J Natl Cancer Inst* 2002; 94:1187–1188.
  25. **Schneider RK, Levenson JL.** Update in psychiatry. *Ann Intern Med* 2002; 137:671–677.
  26. **Brown RP, Gerbarg PL, Muskin PR.** Complementary and alternative treatments in psychiatry. In: Tasman A, Kay J, Lieberman JA, editors. *Psychiatry Therapeutics*, Second Edition. Southern Gate, West Sussex, England: John Wiley and Sons, Ltd, 2003:449–485.
  27. **Whiskey E, Werneke U, Taylor D.** A systematic review and meta-analysis of *Hypericum perforatum* in depression: a comprehensive clinical review. *Int Clin Psychopharmacol* 2001; 16:239–252.
  28. **Ernst E.** The risk-benefit profile of commonly used herbal therapies: ginkgo, St. John's wort, ginseng, echinacea, saw palmetto, and kava. *Ann Intern Med* 2002; 136:42–53.
  29. **Adams KE, Cohen MH, Eisenberg D, Jonsen AR.** Ethical considerations of complementary and alternative therapies in conventional medical settings. *Ann Intern Med* 2002; 137:660–664.
- .....  
**ADDRESS:** Kathleen Franco, MD, Department of Psychiatry, P57, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195.

## CORRECTION

### Asymptomatic hyperparathyroidism

(September 2003)

The article “How should I follow a patient with mildly elevated serum calcium and PTH, but no symptoms?” by Drs. Jennifer Wojtowitz and Christian Nasr (*Cleve Clin J Med* 2003; 70:811–813) contained an error. The article stated that the calcium-

to-creatinine ratio is generally less than 0.01 in familial hypocalciuric hypercalcemia and greater than 0.02 in primary hyperparathyroidism. This should have been the ratio of calcium clearance to creatinine clearance (also known as fractional excretion of calcium). Thanks go to Dr. Juraj Osterman of the University of South Carolina Medical School, Columbia, SC, for pointing this out.