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Parathyroid Hormone in the Evaluation of Hypercalcemia

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A 54-year-old woman was incidentally noted to have hypercalcemia on routine testing. She feels well and reports no concerns. She underwent total thyroidectomy 15 years earlier for papillary thyroid cancer and is taking levothyroxine suppression therapy without evidence of recurrence. Serum calcium levels before her thyroidectomy were normal. She has well-controlled hypertension and hyperlipidemia. Her other medications include losartan, atorvastatin, and ezetimibe. She has no history of low trauma fractures (occurring from falls at standing height or less) or nephrolithiasis. She has no family history of hypercalcemia. Physical examination demonstrated no palpable thyroid tissue. Her laboratory values are reported in the Table.

HOW DO YOU INTERPRET THESE TESTS RESULTS?

A. The patient has familial hypocalciuric hypercalcemia.

B. The patient has hypercalcemia from thyroid suppression therapy.

C. The patient has hypercalcemia of malignancy.

D. The patient has primary hyperparathyroidism.

Answer

D. The patient has primary hyperparathyroidism.

Test Characteristics

The major circulating form of parathyroid hormone (PTH) is the full-length 84-amino acid peptide. Two different PTH assays are available. The second-generation (intact) assay measures PTH (1-84) and large inactive fragments. The third-generation (whole) assay measures only PTH (1-84). Both are equally useful in distinguishing between parathyroid- and nonparathyroid-mediated hypercalcemia.[1] The Medicare reimbursement for either assay is $56.31.

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In primary hyperparathyroidism, PTH levels are generally elevated, although approximately 10% to 20% of individuals will have normal levels by either assay.[1] With hypercalcemia, an intact PTH level of greater than 25 pg/mL is considered abnormal, assuming a normal range of 10 to 65 pg/mL.[2] Nonparathyroid causes of hypercalcemia (eg, malignancy, thyrotoxicosis) present with undetectable or suppressed PTH values. Biotin supplementation may interfere with the PTH immunoassay. Patients with primary hyperparathyroidism who take biotin may have unusually low PTH concentrations.[3]

Application of Test Results to This Patient

The patient has primary hyperparathyroidism on the basis of hypercalcemia, the clinical presentation, and PTH concentration. There are several other etiologies of hypercalcemia that should be considered. Medications such as lithium and thiazides can cause this biochemical profile. Another consideration is familial hypocalciuric hypercalcemia (FHH).[4] FHH is a rare, benign disorder due to loss of function mutations in the calcium-sensing receptor (*CASR*) gene.[5] In FHH, 24-hour urine calcium on a normal calcium diet is usually very low (<100 mg) with a calcium-to-creatinine clearance ratio (CCCR) of less than 0.010. FHH is very unlikely if the calcium-to-creatinine clearance ratio is greater than 0.020. Even if the CCCR is less than 0.010 (as in this case), the patient's total urinary calcium excretion was greater than 100 mg. Primary hyperparathyroidism is still the likely diagnosis. In FHH, there is often a positive family history and patients may present with hypercalcemia at birth, with almost all patients developing hypercalcemia by their third decade. In primary hyperparathyroidism, urinary calcium can be low, normal, or elevated. PTH increases renal tubular calcium reabsorption and urine calcium can be low in individuals with low dietary calcium intake or low 25-hydroxyvitamin D levels. *CASR* gene analysis for known mutations can be considered when the urine calcium level is low and the CCCR is less than 0.020.[1] FHH would be a more serious consideration in this patient if she were younger, had a personal or family history of hypercalcemia, or if both variables were present.

What Are Alternative Diagnostic Approaches?

Both the second- and third-generation PTH assays can differentiate between parathyroid or nonparathyroid etiologies, predominantly primary hyperparathyroidism or malignancy—the 2 most common causes of hypercalcemia.

Patient Outcome

This patient was followed up for 6 years with stable serum calcium levels but progressive declines in bone density. She is now at 2 years following successful parathyroidectomy, with normal serum calcium and PTH values and improvement in skeletal parameters.

Symptomatic patients with nephrolithiasis, fracture, or marked hypercalcemia should be managed surgically. The Proceedings of the Fourth International Workshop on Asymptomatic Primary Hyperparathyroidism were recently published.[1,6–9] Patients with asymptomatic disease are also surgical candidates if any of the following criteria are met: (1) serum calcium of more than 1 mg/dL above the upper limit; (2) creatinine clearance of less than 60 mL/min or marked hypercalciuria with stone risk by urinary biochemical

analysis; (3) T-score of less than −2.5 at the lumbar spine, hip, or distal 1/3 radius; or vertebral fracture by imaging; or (4) age younger than 50 years.[6] The guidelines recommend evaluation for nephrolithiasis in patients who are asymptomatic. Patients not meeting surgical criteria can be monitored with annual or biannual serum calcium and creatinine testing and bone mineral density by dual x-ray absorptiometry every 1 to 2 years. Surgery should be considered if there is a significant decline in bone density. Vitamin D should be repleted, starting with 800 to 1000 IU/day for a minimum serum 25-hydroxyvitamin D level of 20 ng/dL. Guidelines for calcium intake should follow the Institute of Medicine recommendations for the general population (1000–1200 mg/d).[10]

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Clinical Bottom Line

- Primary hyperparathyroidism is characterized by hypercalcemia with elevated or inappropriately normal parathyroid hormone levels.
- The differential diagnosis of primary hyperparathyroidism includes familial hypocalciuric hypercalcemia and hypercalcemia due to lithium or thiazide use.
- Patients with symptomatic hyperparathyroidism should have a parathyroidectomy.
- Asymptomatic patients with hyperparathyroidism should be evaluated for surgery if they are younger than 50 years or meet criteria based on calcium level, renal function, or bone density.[6]

Table

Patient's Laboratory Test Results

Laboratory Test	Patient's Values	Reference Range
Serum calcium, mg/dL	10.7	8.5–10.4
Albumin, g/dL	4.1	3.5–4.9
Intact parathyroid hormone, pg/mL	57.0	10–65
25-Hydroxyvitamin D, ng/mL	44	20–100[a]
Serum creatinine, mg/dL	0.7	0.5–1.2
Thyroid-stimulating hormone, mIU/L	0.03	0.40–5.50
Free thyroxine, ng/dL	1.7	0.8–1.8
24-Hour urine calcium excretion, mg	154	50–300
24-Hour urine creatinine excretion, g	1.34	0.63–2.50
Calcium-to-creatinine clearance ratio[b]	0.008	NA[c]

Abbreviation: NA, not available.

[a] Some experts and organizations recommend a lower normal limit of 25-hydroxyvitamin D of 30 ng/mL and consider the range of 20 to 30 ng/mL as insufficient.

[b] Calcium-to-creatinine clearance ratio = (24-hour urine calcium × serum creatinine) divided by (serum calcium × 24-hour urine creatinine).

[c] A reference range in adults has not been clearly established.