

How should you evaluate elevated calcium in an asymptomatic patient?

Evidence-based answer

First, establish that true hypercalcemia exists by repeating the serum calcium and measuring or calculating the physiologically active serum calcium when abnormalities in blood pH or albumin are found (SOR: **C**, expert opinion). Patients with unexplained asymptomatic true hypercalcemia should be screened for primary hyperparathyroidism (PHPT) and malignancy using an intact parathyroid hormone (PTH) level by

immunoradioassay (SOR: **C**, expert opinion). Other recommended tests that can distinguish PHPT from malignancy and familial hypocalciuric hypercalcemia, as well as help manage patients with PHPT include urinary 24-hour calcium and creatinine levels, parathyroid hormone related peptide (PTHrP), alkaline phosphatase, calcitriol, and bone densitometry (SOR: **C**, expert opinion).

Clinical commentary

Choose tests carefully to reduce false positives

Including serum calcium measurements in the chemistry panels that physicians use to manage common conditions such as hypertension has resulted in an epidemic of incidental hypercalcemia. Tempting as it may be to ignore these unexpected numbers, they point to a significant underlying condition in some patients. This puts the family physician

in a familiar clinical position—having to worry a patient just enough to convince him to consent to a careful, stepwise evaluation while somehow reassuring him that usually no problem is found. The best solution is to order each test for a reason, which would reduce the number of false positives that we spend so much time chasing.

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Evidence summary

Make sure it's true hypercalcemia

Measuring calcium levels in asymptomatic patients often leads to false-positive elevations caused by random error or changes in the level of physiologically active calcium because of alterations in blood pH or serum albumin. Serum calcium levels between 10.0 and 12.0 mg/dL

indicate mild hypercalcemia; levels >14.0 mg/dL are severe. Because changes in pH and serum albumin levels alter levels of physiologically active calcium, authoritative sources recommend measuring or calculating physiologically active calcium if blood pH or albumin is abnormal.^{1,2} To determine the level, use the equation $[4.0 - (\text{plasma albumin})] \times 0.8 + (\text{serum calci-$

TABLE

Causes of hypercalcemia

Primary hyperparathyroidism

Malignancy

- Hematologic cancers (non-Hodgkin's lymphoma, multiple myeloma, leukemia)
- Squamous cell carcinomas (lung, esophagus, cervix, vulva, skin)
- Adenocarcinomas (breast, kidneys, ovaries, bladder)
- Parathyroid carcinoma

Chronic renal failure

Endocrine disorders (hyperthyroidism, pheochromocytoma, Addison's disease)

Familial hypocalciuric hypercalcemia

Immobilization

Laboratory artifact resulting from altered albumin concentration or pH

Medications (vitamin A toxicity [dietary fads, isotretinoin overdose], estrogens, antiestrogens, thiazides, lithium)

Milk alkali syndrome

Vitamin D toxicity (granulomatous disease [sarcoidosis, tuberculosis], vitamin D supplementation)

Based on Hutton E,¹ and Carroll MF et al.²

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A parathyroid hormone-related peptide level >1.0 pmol/L is highly specific for malignancy

um) or measure serum ionized calcium.² Normal levels of serum ionized calcium for adults older than 19 years are 1.13 to 1.32 mmol/L, although the exact range can vary from laboratory to laboratory. Elevated physiologically active calcium indicates true hypercalcemia.

Assess for the most common causes, PHPT and malignancy

Evaluation of the patient with true hypercalcemia should include a detailed history, physical examination, and assessment of risk factors for all causes of hypercalcemia.^{1,2} PHPT and malignancy are the two most common causes of asymptomatic true hypercalcemia (TABLE).²

Laboratory evaluation targeting these causes, beginning with an intact PTH level, is a logical first step.^{1,2} Persistent hypercalcemia in the presence of elevated or inappropriately normal PTH concentrations confirms the diagnosis of PHPT.³ When serum calcium rises, PTH is normally suppressed. Normal intact PTH and low 24-hour urinary calcium excretion distinguishes patients with PHPT from those

with less common familial hypocalciuric hypercalcemia.^{1,2}

Most patients with PHPT are asymptomatic, although some eventually develop bone loss, nephrolithiasis, and renal colic.^{4,5} A 10-year prospective cohort study of patients with PHPT found that 21% of asymptomatic patients developed decreased bone density at one or more sites.⁶ None acquired kidney stones, but hypercalcemia and hypercalciuria did worsen in 10 of 52 patients. A guideline and a review on PHPT recommend measuring creatinine clearance and obtaining a bone densitometry study of the distal third of the radius, hip, and lumbar spine to assess for end-organ changes related to the condition; declining renal function and osteoporosis may be indications for surgery.^{3,5}

Malignancy is the most common cause of low intact PTH and true hypercalcemia, especially when the calcium level is >14 mg/dL.¹ A PTHrP >1.0 pmol/L is highly specific for malignancy because this level does not occur in healthy people.¹ In a prospective case series of patients with hypercalcemia and malignancy, 54% had elevated PTHrP levels.⁷ The authors found that an elevated PTHrP in patients younger than 65 years of age doubles the risk of death from malignancy compared to patients the same age with normal PTHrP (hazard ratio=1.9; 95% CI, 1.1-3.4).

Identify less common causes

Serum calcitriol in association with a low intact PTH level and elevated calcium lower than 14 mg/dL helps differentiate the less common causes of hypercalcemia. Calcitriol is high in granulomatous diseases such as sarcoidosis, tuberculosis, and histoplasmosis, and normal in hyperthyroidism and Addison's disease.¹

Immobilization as a cause of hypercalcemia can be distinguished from PHPT by history and normal PTH levels and from malignancy by a normal alkaline phosphatase level.¹

Recommendations

In addition to the recommendations discussed previously, *Williams Textbook of Endocrinology* advises repeating the initial calcium level twice and measuring serum BUN, creatinine, electrolytes, albumin, globulin, and phosphate.⁸ The authors recommend a generalized work-up for malignancy, including mammography, chest radiography with or without CT, abdominal CT, serum and urine immunoelectrophoresis, and temporary discontinuation of lithium for patients taking the drug. They also recommend using PTHrP only when PTH is suppressed but an underlying malignancy can't be found. ■

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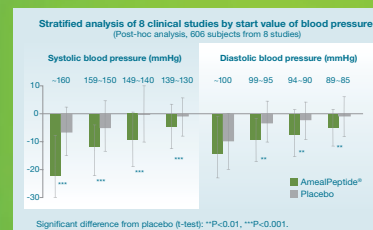
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