

What is the best workup for hypocalcemia?

Evidence-based answer

Unexplained hypocalcemia can usually be diagnosed by a limited number of serum tests when the cause isn't obvious from the history (recent neck surgery or renal failure):

- calcium (corrected for serum albumin)
- creatinine
- phosphorus
- magnesium
- parathyroid hormone (PTH).

The most common causes, categorized according to the results of these tests, are

(strength of recommendation: **C**, expert opinion, case series, and physiologic principles):

- high PTH, high phosphorus, and high creatinine: renal failure
- high PTH, low or normal phosphorus, and normal creatinine: vitamin D deficiency or pancreatitis
- low PTH, high phosphorus, and normal creatinine: inadequate parathyroid gland function or hypomagnesemia.

Clinical commentary

Important supporting tests—serum albumin, phosphorus, magnesium

Serious abnormal laboratory results often are encountered in outpatient testing using multitest panels such as basic and comprehensive metabolic profiles. Hypocalcemia found on a basic metabolic panel is a good example of such a result.

Given the broad differential diagnosis outlined by the authors of this Clinical Inquiry, we must interpret abnormal results with the proper supporting tests. In this case, the most important is serum albumin, which can be a critical

indicator of whether the patient truly has hypocalcemia. That is why I tend to order a comprehensive metabolic panel when disorders of calcium metabolism are part of the differential.

This Clinical Inquiry also highlights the important role of phosphorus and magnesium in calcium metabolism. It's important to note that these tests are no longer a regular component of many multitest blood panels and must be ordered when hypocalcemia is found.

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Evidence summary

Normal values for total or corrected serum calcium are 8.5-10.2 mg/dL and for ionized calcium, 4.4-5.4 mg/dL. Because total serum calcium is approximately 50% free (ionized) and 50% bound, pri-

marily to albumin, the serum level must be "corrected" if hypoalbuminemia exists. Because serum calcium comprises less than 1% of body stores, severe total body deficiency of calcium can exist without hypocalcemia.^{1,2}

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Because serum calcium comprises less than 1% of body stores, severe total body calcium deficiency can exist without hypocalcemia

Ionized calcium is under tight physiologic control, monitored by calcium-sensing proteins in the parathyroid gland; low ionized calcium augments PTH secretion, which in turn has 3 primary actions:

- decreased calcium excretion by the kidneys
- increased activity of osteoclasts, leading to calcium release from bone
- increased activity of renal 25-OH vitamin D hydroxylase, resulting in elevated serum levels of calcitriol, the active form of vitamin D; elevated calcitriol in turn augments gastrointestinal absorption of calcium.

An adequate supply of 25-OH vitamin D to the kidneys requires adequate gastrointestinal absorption or sun-induced skin production of vitamin D and sufficient liver function to carry out the first of the 2 hydroxylation steps.^{1,3}

Common causes of hypocalcemia

We found no studies that established the frequency of various causes of hypocalcemia in the general population, but reviewers concurred that the most common specific causes, in order of frequency, are (TABLE):^{2,3}

- renal failure
- vitamin D deficiency
- hypomagnesemia
- pancreatitis
- hypoparathyroidism.

It is not surprising that renal failure is a common cause of hypocalcemia, given the high prevalence of chronic kidney disease in adults—11.2% of the total United States population older than 20 years has at least a mildly reduced glomerular filtration rate (stage 2, chronic kidney disease, with glomerular filtration rate <90 cc/min).⁴ Despite elevated PTH, serum calcium may be slightly reduced (and osteomalacia present) even in mild chronic kidney disease.^{5,6} Only severe or end-stage chronic kidney disease (glomerular filtration rate <30 cc/min, 5.8% of population) is often associated

with actual hypocalcemia.^{5,6} Likewise, the prevalence of vitamin D deficiency (<15 ng/mL of 25-OH vitamin D) is 35% to 55% in the general population,^{7,8} and 95% in institutionalized elderly patients.⁹

Chronic kidney disease (66%) and vitamin D deficiency (24%) were the most common causes of hypocalcemia in a study of 594 elderly general medicine inpatients.¹⁰ In a study of 62 hypocalcemic patients in a medical intensive care unit, the cause of the hypocalcemia could be determined in only 28 (45%); most of the cases were caused by hypomagnesemia (28%), renal insufficiency (8%), and pancreatitis (3%).¹¹

Serious causes of hypocalcemia

The usual cause of critically low serum calcium (<7 mg/dL “corrected” or <3.2 mg/dL ionized) is parathyroidectomy or acute renal failure. Hypocalcemia resulting from partial parathyroidectomy or thyroidectomy (with inadvertent parathyroidectomy) occurs in approximately 5% of these surgeries; 99.5% of cases resolve completely within a year.¹²

Recommendations

Several reviewers recommend a similar workup and differential diagnosis for hypocalcemia. Unfortunately, none cites quantitative data on the prevalence of hypocalcemia and its causes.^{2,13}

Some authors recommend measuring 25-OH vitamin D in all hypocalcemia patients with elevated PTH without hyperphosphatemia to confirm vitamin D deficiency.^{1,2} Others emphasize the importance of measuring ionized calcium to detect hypocalcemia, especially in critically ill patients, in whom many acute variables can decrease ionized calcium (alkalosis can increase protein binding, for example).^{1,3,14}

Although several reviewers present an algorithmic approach to determining the cause of hypocalcemia,³ we could find no data on the derivation or vali-

TABLE

Causes of hypocalcemia by key test results

| TEST RESULTS | COMMON CAUSES | LESS COMMON CAUSES |
|----------------------------------|---|---|
| High PTH, high phosphorus | Renal failure | <ul style="list-style-type: none"> • Pseudohypoparathyroidism (unresponsiveness to PTH) • Other hyperphosphatemic states (eg, rhabdomyolysis or massive tumor lysis) |
| High PTH, low phosphorus | Vitamin D deficiency (with low bone calcium) caused by: <ul style="list-style-type: none"> • inadequate diet or lack of sunlight • gastrointestinal malabsorption, including drug-induced malabsorption (cholestyramine) • hepatobiliary disease and hepatic drug metabolism • pancreatitis | <ul style="list-style-type: none"> • Blood transfusions (citrate) • Bisphosphonates • End organ unresponsiveness to vitamin D • Congenital absence of renal vitamin D hydroxylase |
| Low PTH, high phosphorus | Hypoparathyroidism and hypomagnesemia | <ul style="list-style-type: none"> • Thyroid and parathyroid surgery • Autoimmune disorder (polyglandular syndrome) • Hypothyroidism • Damage to parathyroid gland from invasion or infiltration (eg, tumor) or radiation • Inherited hypoparathyroidism |

PTH, parathyroid hormone.

ation of the diagnostic effectiveness of these algorithms. ■

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The most common causes of hypocalcemia:

- renal failure
- vitamin D deficiency
- hypomagnesemia
- pancreatitis
- hypoparathyroidism