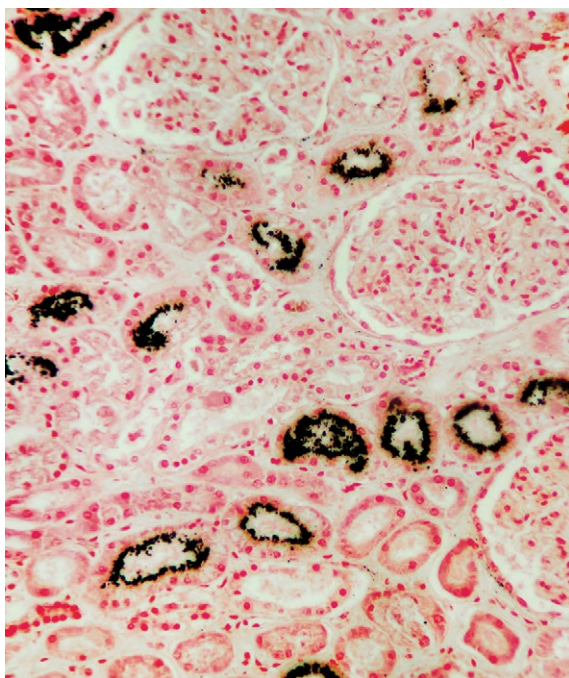


Lithium-associated hypercalcemia: Monitoring and management



JABAL HARSHAW/SHUTTERSTOCK

Regular monitoring of calcium levels in patients receiving lithium can improve outcomes

Hypercalcemia is a well-known but underrecognized adverse effect of lithium. Most patients with lithium-associated hypercalcemia (LAH) have either non-specific symptoms (eg, persistent tiredness, constipation, polyuria, polydipsia) or no symptoms. Clinically, LAH differs from primary hyperparathyroidism, though the management protocol of these 2 conditions is almost the same. In this article, we discuss how lithium can affect calcium and parathyroid hormone (PTH) levels and how LAH and lithium-associated hyperparathyroidism (LAHP) differs from primary hyperparathyroidism. We also outline a suggested approach to monitoring and management.

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An insidious problem

Due to the varying definitions and methods used to assess hypercalcemia, the reported prevalence of LAH varies from 4.3% to 80%.¹ McKnight et al² conducted a systematic review and meta-analysis of studies of the relationship between lithium and parathyroid function that included 14 case-control studies, 36 case reports, and 6 cross-sectional studies without a control group. They found that the levels of calcium and PTH were 10% higher in lithium-treated patients than in controls.²

Pathophysiology. Lithium is known to increase both calcium and PTH levels. PTH is responsible for calcium homeostasis.

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Table 1

Difference between primary hyperparathyroidism and lithium-associated hyperparathyroidism

Primary hyperparathyroidism	Lithium-associated hyperparathyroidism
Hypercalcemia	Variable hypercalcemia
Low phosphate levels	Normal phosphate levels
Hypercalciuria	Hypocalciuria
Increased bone resorption	Decreased bone resorption
Most patients present with single adenoma	Can present with either single or multiglandular disease
Progressive course	Transient or progressive course

Source: References 1,3,4

It is secreted in response to low calcium levels, which it increases by its action on bones, intestines, and kidneys. Vitamin D also plays a crucial role in calcium homeostasis. A deficiency of vitamin D triggers a compensatory increase in PTH to maintain calcium levels.³

Calcium and PTH levels increase soon after administration of lithium, but the rise is usually mild and insidious. In a small proportion of patients who receive long-term lithium treatment, calcium levels can exceed the normal range. Patients who develop LAH typically have serum calcium levels slightly above the normal range and PTH levels ranging from the higher side of the normal range to several times the upper limit of the normal range. Patients might also experience elevated PTH levels without any increase in calcium levels. Lithium can affect calcium and PTH levels in multiple ways. For instance, it increases the reabsorption of calcium in the kidney as well as the reset point of calcium-sensing receptors. Therefore, only higher levels of calcium can inhibit the release of PTH. Hence, in cases where the PTH level is within the normal range, it is generally higher than would be expected for a given serum calcium level. Lithium can also directly affect the parathyroid glands and can lead to either single-nodule or multimodule hyperplasia.⁴

Long-term lithium use can cause chronic kidney disease (CKD), which in turn leads to vitamin D deficiency and hyperparathyroidism. However, secondary hyperparathyroidism with CKD is usually seen in the more advanced stages of CKD, and

is associated with low-to-normal calcium levels (as opposed to the high levels seen in LAH).³⁻⁵

Lithium-associated hyperparathyroidism

Primary hyperparathyroidism is the most common cause of hypercalcemia. Its prevalence ranges from 1 to 7 cases per 1,000 adults. The incidence of LAH/LAHP is 4- to 6-fold higher compared to the general population.⁶ Similar to LAH/LAHP, primary hyperparathyroidism is more common in older adults (age >60) and females. Hence, some researchers have suggested that lithium probably unmasks hyperparathyroidism in patients who are susceptible to primary hyperparathyroidism.³

Look for these clinical manifestations

Symptoms of primary hyperparathyroidism are related to high calcium and PTH levels. They are commonly described as “painful bones, renal stones, abdominal groans (due to hypercalcemia-induced ileus), and psychic moans (lethargy, poor concentration, depression).” Common adverse outcomes associated with primary hyperparathyroidism are renal stones, high risk of fracture, constipation, peptic ulcer, and pancreatitis.^{3,7}

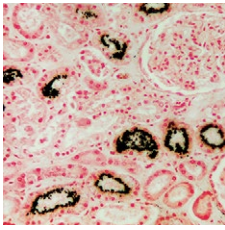
In contrast, LAHP is characterized by mild, intermittent, and/or persistent hypercalcemia and mildly increased PTH (Table 1).^{1,3,4} In some patients, it could

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Calcium and parathyroid hormone levels increase soon after administration of lithium, but the rise is usually mild



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Lithium and calcium

Clinical Point

In most cases, LAH is an insidious adverse effect that is usually detected on blood tests after many years of lithium therapy

Table 2

Categorization of adjusted calcium levels

Category	Range
Normal	2.2 to 2.5 mmol/L
Mild hypercalcemia (often asymptomatic)	2.5 to 3 mmol/L
Moderate hypercalcemia	3 to 3.5 mmol/L
Severe hypercalcemia (a medical emergency)	>3.5 mmol/L

Source: Reference 5

improve without active intervention. Because lithium increases the absorption of urinary calcium, it is associated with hypocalciuria and a lower risk of renal stones. Additionally, lithium has osteoprotective effects and has not been associated with an increased risk of fracture. Some researchers have suggested that the presentation of LAHP is more like familial hypocalciuric hypercalcemia (FHC), which is also associated with hypocalciuria. FHC is a benign condition and does not require active intervention.^{3,4} Similar to those with FHC, many patients with LAHP may live with chronic asymptomatic hypercalcemia without any significant adverse outcome.

A suggested approach to monitoring

In most cases, LAH is an insidious adverse effect that is usually detected on blood tests after many years of lithium therapy.⁸ For patients starting lithium therapy, International Society of Bipolar Disorder guidelines recommend testing calcium levels at baseline, 6 months, and annually thereafter, or as clinically indicated, to detect and monitor hypercalcemia and hyperparathyroidism. However, these guidelines do not provide any recommendations regarding how to manage abnormal findings.⁹

Clinical laboratories report both total and adjusted calcium values. The adjusted calcium value takes into account albumin levels. This is a way to compensate for an abnormal concentration of albumin (establishing what a patient's total calcium concentration would be if the albumin concentration was normal). *Table 2*⁵ shows

the categorization of adjusted calcium values. For patients receiving lithium, some researchers have suggested monitoring PTH as well as calcium.¹

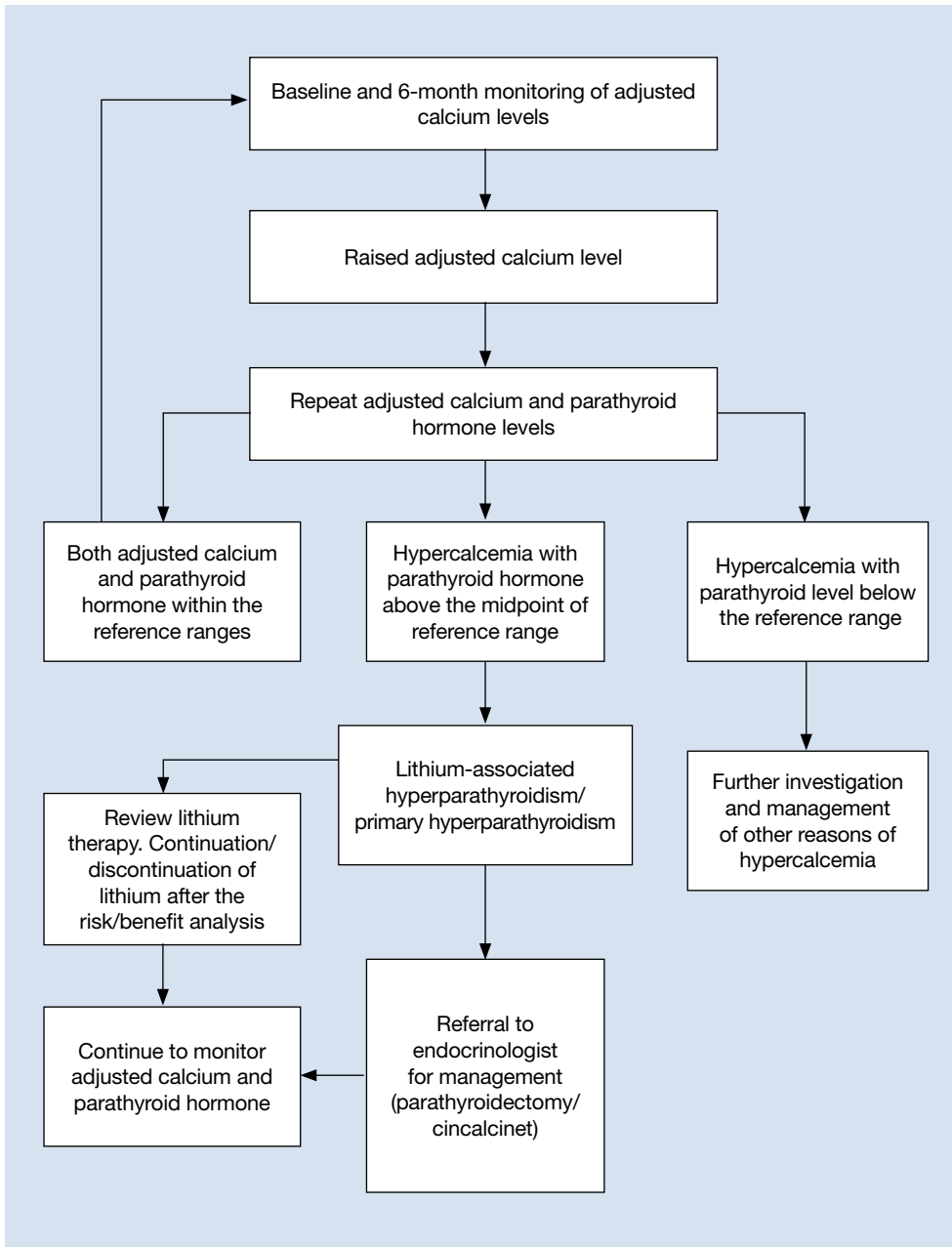
The *Figure (page 39)* outlines our proposed approach to monitoring for LAH in patients receiving lithium. An isolated high value of calcium could be due to prolonged venous stasis if a tourniquet is used for phlebotomy. In such instances, the calcium level should be tested again without a tourniquet.¹⁰ If the repeat blood test shows elevated calcium levels, then both PTH and serum calcium should be tested.

If the PTH level is higher than the midpoint of the reference range, LAH should be suspected, though sometimes hypercalcemia can present without raised PTH. LAH has also been reported to cause a transient increase in calcium levels. If hypercalcemia frequently recurs, PTH levels should be monitored. If PTH is suppressed, then the raised calcium levels are probably secondary to something other than lithium; common reasons for this include the use of vitamin D supplements or thiazide diuretics, or malignancies such as multiple myeloma.^{3,5,8}

Treatment: Continue lithium?

There are several options for treating LAH. Lithium may be continued or discontinued following close monitoring of calcium and PTH levels, with or without active interventions such as surgery or pharmacotherapy, and as deemed appropriate after consultation with an endocrinologist. The decision should be informed by evaluating the risks and benefits to the patient's physical and mental health. LAH

Monitoring for lithium-associated hypercalcemia



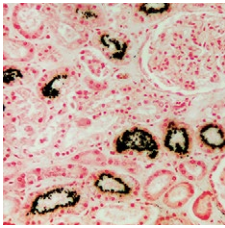
Clinical Point

The primary treatment of LAH and primary hyperparathyroidism is parathyroidectomy

can be reversed by discontinuing lithium, but this might not be the case in patients receiving long-term lithium therapy, especially if their elevated calcium levels are associated with parathyroid adenomas or hyperplasia. Hence, close monitoring of calcium and PTH is required even after discontinuing lithium.^{3,8}

Surgical treatment. The primary treatment of LAH and primary hyperparathyroidism

is parathyroidectomy. The possibility of recovery after parathyroidectomy for primary hyperparathyroidism is 60% to 80%, though a small proportion of patients might experience recurrence. This figure might be higher for LAH, because it is more likely to affect multiple glands.^{1,11} Other potential complications of parathyroidectomy are recurrent laryngeal nerve injury causing paralysis of vocal cords



Lithium and calcium

Clinical Point

Pharmacotherapy with cinacalcet is an option for patients who are not candidates for or do not want surgery

Related Resources

- Laski M, Foreman R, Hancock H, et al. Lithium: an underutilized element. *Current Psychiatry*. 2021;20(12):27-30,34. doi:10.12788/cp.0193
- Pelekanos M, Foo K. A resident's guide to lithium. *Current Psychiatry*. 2021;20(4):e3-e7. doi:10.12788/cp.0113

Drug Brand Names

Cinacalcet • Sensipar

leading to hoarseness of voice, stridor, or aspiration, and local hematoma and hypocalcemia (requiring vitamin D and/or calcium supplements).¹²

Pharmacotherapy. Cinacalcet is a calcimimetic drug that decreases the reset point of the calcium-sensing receptor. It can be used if a patient is not suitable for or apprehensive about surgical intervention.^{1,8}

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Bottom Line

Calcium levels should be regularly monitored in patients receiving lithium. If calcium levels are persistently high, parathyroid hormone levels should also be measured. Management of lithium-associated hypercalcemia includes watchful waiting, discontinuing lithium, parathyroidectomy, and pharmacotherapy with cinacalcet.