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# Lithium treatment and hyperparathyroidism: Clinical implications and management

Roberto Lozano [1,*] and Carina Bona [2]

[1] *Department of Pharmacy, University clinical hospital"Lozano Blesa", Zaragoza, Spain.*
[2] *Unit for the Rational Use of Medicines, Aragon Health Service, Zaragoza, Spain.*

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## Abstract

**Objective**: To analyze the association between chronic lithium treatment and hyperparathyroidism, exploring pathophysiological mechanisms, clinical manifestations, diagnostic approaches, and management strategies.

**Methods**: A review of clinical cases and literature evidence is presented, integrating findings from real-world psychiatric populations.

**Results**: Lithium use was associated with elevated serum calcium and parathyroid hormone (PTH) levels, increasing the risk of nephrolithiasis, osteoporosis, and cardiovascular complications.

**Discussion**: Hyperparathyroidism secondary to lithium therapy represents a significant but often overlooked adverse effect. Its detection requires systematic biochemical monitoring and clinical awareness. Conclusion: Regular calcium and PTH assessments are recommended in patients receiving lithium, with individualized management strategies including dose adjustment, medical therapy, or parathyroidectomy in selected cases.

**Keywords:** Lithium; Hyperparathyroidism; Bipolar disorder; Calcium metabolism; Endocrine side effects

## 1. Introduction

Lithium salts remain a cornerstone in the management of bipolar disorder, particularly for maintenance treatment and relapse prevention. Since their introduction in the mid-20th century, lithium compounds have been demonstrated to reduce the frequency of manic and depressive episodes and to exert a protective effect against suicide. Their clinical utility, however, is tempered by a narrow therapeutic index and a spectrum of potential adverse effects. Among these, disturbances in mineral metabolism and parathyroid function are increasingly recognized as relevant concerns [1].

Hyperparathyroidism induced or exacerbated by lithium therapy has been reported in up to 10% of long-term users, though prevalence estimates vary considerably depending on the studied population and diagnostic thresholds [2]. The underlying mechanism appears to involve lithium's modulation of the calcium-sensing receptor (CaSR) on parathyroid cells, which alters the set point for serum calcium regulation. This shift results in higher serum calcium concentrations being required to suppress parathyroid hormone (PTH) secretion, leading to persistent elevation of both calcium and PTH [3].

The clinical consequences of lithium-associated hyperparathyroidism are multifaceted. Chronic hypercalcemia can manifest as nephrolithiasis, polyuria, gastrointestinal disturbances, neurocognitive symptoms, and bone ineralization. Long-term, patients may face increased risks of osteoporosis, cardiovascular morbidity, and reduced quality of life [4].

* Corresponding author: Roberto Lozano

Despite these risks, awareness among psychiatrists and general practitioners remains limited, resulting in underdiagnosis and delayed treatment.

In addition, lithium-induced hyperparathyroidism poses complex therapeutic challenges. While discontinuation of lithium often ameliorates hypercalcemia, such a strategy is not always feasible due to the risk of psychiatric destabilization. Alternative approaches, including pharmacological interventions with calcimimetics such as cinacalcet, vitamin D supplementation, or surgical parathyroidectomy, may be required in refractory cases [5].

This article expands upon preliminary findings presented at the 15th Virtual Congress of Psychiatry (Interpsiquis 2014), providing an updated and detailed overview of lithium-associated hyperparathyroidism. We aim to contextualize its pathophysiology, clinical presentation, diagnostic strategies, and management within contemporary psychiatric practice, thereby equipping clinicians with practical guidance for monitoring and treatment.

## 2. Materials and Methods

This article integrates data from a case series of patients undergoing lithium therapy with biochemical abnormalities suggestive of hyperparathyroidism, alongside a review of published literature. Patients were selected from psychiatric outpatient clinics where long-term lithium monitoring protocols were in place. Inclusion criteria included a diagnosis of bipolar disorder type I or II according to DSM-5 criteria, continuous lithium therapy for at least 12 months, and availability of biochemical data, including serum calcium and PTH levels. Exclusion criteria comprised primary hyperparathyroidism unrelated to lithium use, renal insufficiency stage ≥3, or concurrent use of medications affecting calcium metabolism such as thiazide diuretics.

Clinical assessments included psychiatric evaluation, physical examination, and biochemical monitoring at baseline and during follow-up. Laboratory tests comprised serum calcium (total and ionized), PTH, vitamin D, renal function tests (creatinine, eGFR), and bone turnover markers. Bone mineral density was measured in selected cases using dual-energy X-ray absorptiometry (DEXA). Imaging studies, including neck ultrasound or sestamibi scans, were performed when parathyroidectomy was considered.

The literature review was conducted using PubMed, Scopus, and Embase databases, with search terms including "lithium," "hyperparathyroidism," "calcium," and "bipolar disorder." Articles published between 1990 and 2024 were screened, prioritizing observational studies, case reports, and systematic reviews. Data extracted included prevalence estimates, mechanisms of action, clinical outcomes, and treatment strategies.

Statistical analysis for the case series involved descriptive statistics. Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. Given the exploratory nature and small sample size, no inferential statistical tests were applied. Instead, emphasis was placed on identifying patterns consistent with published evidence.

Ethical approval was obtained from the institutional review board, and all patients provided informed consent for the use of their anonymized data in research and publication.

## 3. Results

The case series included 12 patients with bipolar disorder (7 females, 5 males) aged 32–68 years (mean age 49 ± 12 years) who had been treated with lithium for a mean duration of 8.5 ± 4.2 years. All patients had therapeutic lithium plasma levels within the recommended range (0.6–1.2 mmol/L).

Biochemical analyses revealed elevated serum calcium in 9 patients (75%), with mean total calcium of 10.8 ± 0.6 mg/dL (reference range 8.5–10.5 mg/dL). PTH levels were elevated in 10 patients (83%), with mean values of 95 ± 30 pg/mL (reference 10–65 pg/mL). Three patients (25%) had reduced vitamin D levels (<20 ng/mL), which may have further contributed to secondary alterations in calcium metabolism. Renal function was preserved in all cases (mean eGFR 82 ± 12 mL/min/1.73m$^2$).

Clinical manifestations included fatigue (67%), polyuria and polydipsia (50%), cognitive complaints such as memory impairment (42%), and musculoskeletal pain (33%). Two patients developed nephrolithiasis confirmed by imaging, while one patient demonstrated reduced bone mineral density on DEXA consistent with osteopenia.

Lithium discontinuation was attempted in four patients; in two cases, this led to normalization of calcium and PTH levels within six months, though psychiatric relapse necessitated reintroduction of lithium. Two patients underwent surgical parathyroidectomy, both with histologically confirmed parathyroid hyperplasia. Postoperatively, calcium and PTH levels normalized, with no recurrence observed over two years of follow-up.

Adjunctive medical therapy with cinacalcet was initiated in two patients who were unable to discontinue lithium and who had persistent hypercalcemia. Both demonstrated significant reductions in calcium and PTH within three months of treatment, with clinical improvement in symptoms of fatigue and polyuria. However, one patient discontinued cinacalcet due to gastrointestinal intolerance.

The literature review identified more than 200 publications addressing lithium and hyperparathyroidism, including cohort studies reporting prevalence rates of 4–10%. Meta-analyses confirmed a consistent association, with lithium-treated patients having a threefold increased risk of hypercalcemia compared with psychiatric controls not exposed to lithium [6]. Case reports and small series emphasized the variable clinical spectrum, ranging from asymptomatic hypercalcemia detected on routine testing to severe complications such as osteoporosis and kidney stones.

## 4. Discussion

The findings of this study highlight the strong association between chronic lithium therapy and disturbances in calcium-parathyroid homeostasis. The high prevalence of hypercalcemia and elevated PTH in our case series is consistent with previously reported rates and reinforces the need for systematic monitoring in lithium-treated populations. The pathophysiological mechanism most widely accepted involves lithium's effect on the calcium-sensing receptor (CaSR), which increases the threshold for calcium-mediated suppression of PTH secretion [3]. This leads to parathyroid hyperplasia and, in some cases, adenoma formation. Chronic exposure results in persistent hyperparathyroidism, even in patients with therapeutic lithium levels.

The clinical spectrum is broad, ranging from subtle cognitive symptoms and fatigue to nephrolithiasis and osteoporosis. Importantly, hyperparathyroidism may exacerbate mood instability, creating diagnostic challenges in psychiatric populations. Symptoms such as irritability, depression, and cognitive dysfunction may overlap with the underlying psychiatric disorder, leading to underrecognition of the endocrine contribution [7].

Management of lithium-induced hyperparathyroidism requires careful consideration of psychiatric stability. Discontinuation of lithium may normalize calcium metabolism but carries significant risk of mood relapse. In our series, two patients experienced psychiatric destabilization following lithium withdrawal, necessitating its reintroduction. This underscores the need for individualized decision-making, balancing psychiatric and endocrine outcomes. Surgical parathyroidectomy remains the definitive treatment in refractory cases, with high success rates. Our findings, consistent with prior reports, suggest that histological examination frequently reveals parathyroid hyperplasia rather than solitary adenomas [8].

Pharmacological interventions such as cinacalcet offer a valuable alternative for patients in whom lithium discontinuation is not feasible. Cinacalcet acts as a calcimimetic, enhancing the sensitivity of CaSR to extracellular calcium and thereby reducing PTH secretion. Clinical trials in primary hyperparathyroidism have demonstrated efficacy, and case reports support its use in lithium-associated hyperparathyroidism [9]. However, tolerance and long-term safety remain areas requiring further study.

From a clinical practice perspective, our results highlight the importance of routine biochemical monitoring. Baseline and periodic assessments of serum calcium, ionized calcium, and PTH should be incorporated into standard lithium monitoring protocols, alongside renal and thyroid function. Vitamin D status should also be evaluated, as deficiency may worsen calcium imbalance and contribute to skeletal complications. Interdisciplinary collaboration between psychiatrists, endocrinologists, and primary care providers is critical for optimizing patient outcomes.

The literature review confirms the global relevance of this issue, with consistent findings across geographic regions. Yet, awareness among clinicians remains limited. Educational initiatives are needed to ensure early recognition and appropriate management. At a research level, large-scale prospective studies are required to clarify the incidence, long-term outcomes, and cost-effectiveness of routine screening. Genetic and pharmacogenomic studies may also elucidate individual susceptibility to lithium-induced parathyroid dysfunction.

Our study is limited by its small sample size and observational design. Nevertheless, the consistency of our findings with published data enhances confidence in the conclusions. Further research is warranted to refine diagnostic criteria, identify predictors of risk, and evaluate preventive strategies.

## 5. Conclusion

In conclusion, lithium therapy, while highly effective for mood stabilization in bipolar disorder, is associated with a significant risk of hyperparathyroidism and hypercalcemia. Our case series, supported by a broad review of the literature, confirms that this complication is common and clinically relevant. Regular monitoring of calcium and PTH levels is essential, particularly in patients receiving long-term therapy. Management strategies must be individualized, balancing the risks of psychiatric relapse with the need to prevent endocrine and systemic complications. Options include lithium dose adjustment, adjunctive pharmacological therapy such as cinacalcet, and surgical parathyroidectomy in refractory cases. Ultimately, collaborative care between psychiatry and endocrinology is vital to ensure safe and effective treatment. By increasing awareness and integrating preventive monitoring into routine practice, clinicians can reduce the burden of lithium-associated hyperparathyroidism and improve outcomes for patients with bipolar disorder.

## Compliance with ethical standards

### *Disclosure of conflict of interest*

No conflict of interest to be disclosed.

### *Statement of informed consent*

Informed consent was obtained from all individual participants included in the study.

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